ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY

FOUNDED BY JAMES PLEASANT PARKER

VOLUME 52

Published Quarterly
BY THE
ANNALS PUBLISHING COMPANY
EDITORIAL OFFICE . 1010 BEAUMONT BLDG., 8
BUSINESS OFFICE . 7200 WYDOWN BL., 5
ST. LOUIS, MO., U.S.A.

Annual Subscription in United States, Spain, Central and South America, $6.00 in Advance. Canada, $6.40. Other Countries, $6.80.

Table of Contents, Volume 52

MARCH, 1943—NUMBER 1

JUNE, 1943—NUMBER 2

SEPTEMBER, 1943—NUMBER 3

DECEMBER, 1943—NUMBER 4

Contents.

ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY

FOUNDED BY JAMES PLEASANT PARKER

VOLUME 52

Published Quarterly

BY THE

ANNALS PUBLISHING COMPANY

EDITORIAL OFFICE . 1010 BEAUMONT BLDG.
BUSINESS OFFICE . 7200 WYDOWN BL.

ST. LOUIS, MO., U.S.A.

Annual Subscription in United States, Spain, Central and South America, $6.00 in Advance. Canada, $6.40. Other Countries, $6.80.

Contents.

CONTENTS—Continued

ANNALS
OF
OTOLOGY, RHINOLOGY
AND
LARYNGOLOGY

VOL. 52 MARCH, 1943 No. 1

I

THE RELATION OF CILIARY INSUFFICIENCY TO DEATH FROM ASTHMA AND OTHER RESPIRATORY DISEASES*†

A. C. HILDING, M.D.

DULUTH, MINN.

Death may result from physiologic failure of any one of a number of systems, such as the urinary, circulatory, or central nervous systems. Death may also occur from failure of the ciliary system within the respiratory tract, a fact which has apparently received little, if any, attention. In certain diseases of the lower respiratory tract, the cilia become destroyed and ciliary function is lost. Secretions collect, as a result, in such large quantities that the patients die of asphyxia.

My interest in the subject is rather accidental. Some years ago I published the results of some experimental work on the nose in which one nostril of a group of rabbits was permanently closed surgically.[1] An unexpected change was observed on the closed side. There was a more or less complete metamorphosis of the ciliated epithelium. It had changed to secreting epithelium. The erstwhile ciliated columnar cells were all goblet cells and quite devoid of cilia. This finding was recorded in 1932 without any attempt to explain it. Six years later I sat in a clinical-pathological conference listening to

*From the Department of Pathology, University of Minnesota.

†Read before the American Academy of Ophthalmology and Otolaryngology, October 12, 1942.

the pathologist's report on a fatal case of asthma. He described at some length the accumulation of thick mucus in the bronchial tree which had asphyxiated the patient, "because it had been too heavy for the tract to remove". That concept did not agree with the results of some tests that we had done at the Mayo Foundation.[2] We had found thick, tenacious mucus to be the type of secretion which the ciliary system conveyed most readily, especially upon vertical surfaces. The pathologist then projected a section of bronchiole upon the screen, and there was the same picture that had occurred in the nasal epithelium of our rabbits behind the closed nostril. Every ciliated cell had become a goblet cell. After the meeting, we went over the sections together and found that this metamorphosis was so extensive that there were scarcely any cilia to be found. Apparently the patient had been asphyxiated by the secretion, not because it was too heavy to be removed, but because the mechanism designed to remove it had been destroyed.

Since then I have read a number of textbooks, and only one mentioned the change of ciliated to mucus-producing cells.[3] Twelve of the fatal asthma cases reviewed at the University of Minnesota showed this change, but it was mentioned in only one of the necropsy reports.

Huber and Koessler[4] published a very comprehensive article on the pathology of asthma in 1922. They reviewed all of the fatal cases described in the literature up to that time (15 in number) and added 6 of their own, making a total of 21. All of these 21 cases had been thoroughly studied clinically and pathologically. Increase of goblet cells in the bronchial epithelium is mentioned in five cases. Two of these were reported by Marchand[5] and three by Huber and Koessler. Yet in each instance the change is just mentioned, without description or amplification of any kind. Each of the 21 reports is followed by a comment giving "the most significant pathological changes." In none of them is the change from cilated to goblet cells listed. Nor in the discussion and summary at the end of the article is any mention made of this striking change in the epithelium. Fraenkel,[6] in a case report from the year 1900, makes one interesting and significant statement: "The ciliated cells are elongated, and the ciliated border in some is ruptured, and the mucus content protrudes in the lumen like a drop, often fusing with neighboring drops."

Several articles in the literature have made scanty mention of changes in the epithelium since 1922. For instance, Fowler[7] in a caption has this phrase "and hyperactivity of lining cells"; Craige[8]

describes degeneration of the mucous glands; Bubert and Warner[9] state that there is "some degeneration and desquamation"; Michael and Rowe[10] state that the epithelium is flattened and thinned; MacDonald[11] speaks of some ulceration and hypertrophy and folding of the mucosa; Lamson and Butt,[12] in a caption, point out partial desquamation and "rather marked mucoid degeneration" but make no mention of it in the text. Steinberg[13] makes a statement that there is a metaplasia from columnar to squamous epithelium. In two articles there are good photomicrographs of bronchioles that show the metamorphosis, but it is not mentioned by the author in either. Jorgensen,[14] in 1936, reported the pathological findings in three fatal cases of asthma with meticulous care. He includes a very fine description of this change, and, in my opinion, establishes it as a true metamorphosis* of the individual ciliated cell and not simply a replacement by a mucus-producing cell. Even he, however, fails to mention the loss of cilia and the role that this might have played in the death of his patients.

In a word, this extensive change in the bronchial epithelium that occurs in fatal cases of asthma, although known and described, does not seem to be generally known, nor does its fatal possibilities seem to be in the least appreciated. The loss of ciliary function is not even mentioned in any textbook or article which I have been able to find. It seems to me that this subject is worthy of careful study and comprehensive discussion.

This present study was undertaken in the hope of learning something about the role of the ciliary mechanism in a number of diseases of the lower respiratory tract, such as asthma, acute tracheobronchitis, postoperative atelectasis, influenzal pneumonia, bronchopneumonia, lobar pneumonia, and bronchiectasis. Only in the case of asthma, however, are results sufficiently definite so that one can speak with some degree of certainty. Beginnings have been made in some of the others, and some very promising experimental results have been obtained, but only comments in progress can be made on these as yet.

Let us consider briefly the physiology of removal of secretion from the lower respiratory tract. The ciliary mechanism is similar to that in the nose and sinuses, and is doubtless largely responsible—perhaps solely responsible—for the removal of secretion under nor-

*The metamorphosis is retrograde or degenerative because the cell apparently is completely destroyed in the process of producing the secretion. It is supposed that true goblet cells rebuild after secretion and secrete again.

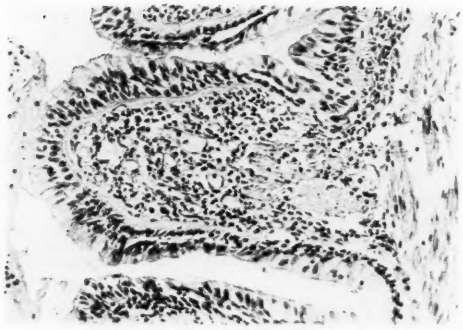


Fig. 1.—Low power photomicrograph of the bronchiolar epithelium in a fatal case of asthma of six years' duration. Practically all of the cells are nonciliated secreting cells instead of the ciliated cells normally found in this epithelium. A few ciliated cells are found deep in the folds. The folding indicates constriction of the bronchiole.

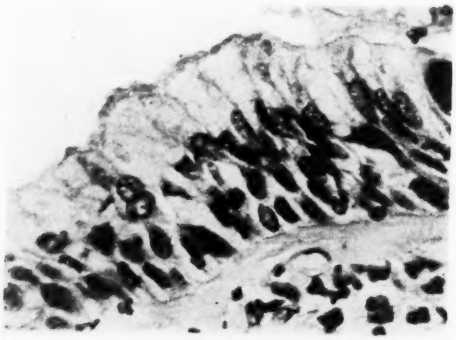


Fig 2.—High magnification of a field from Fig. 1.

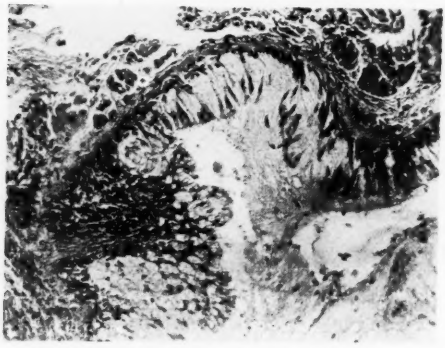


Fig. 3.—The group of epithelial cells in the right center have become mucin-producing cells. Note how the mucus strand which has been secreted has fused with the mass in the lumen but remains attached deep within the cells which produced it. Some of the nuclei look as though they had been dragged out of position by traction. There are still some ciliated cells remaining on both sides of the mucus strand.

mal conditions. Unlike the nose, the lungs are compressible and are in motion. Consequently, a number of other factors may enter in. The lungs, when fully expanded, contain about 4700 cc. of air. Forced expiration reduces this volume to about 1000 cc. or 1500 cc. Moreover, the bronchioles and bronchi, which cannot be collapsed on account of cartilaginous rings, can be shortened axially. If there is much secretion in the lungs, this reduction in volume by two-thirds would tend to force it up into the larger air passages. It would tend to cling there during the next inspiration, especially if it were mucinous, even though it were forced back somewhat. Coughing is another means of aiding in the removal of excess secretion. The air is inspired slowly enough so that resistance to its passage is low. It is expired explosively and flows out at such a high rate of speed that the contained secretion is carried out by the blast. Air resistance increases as the square of the speed. One gets the impression when making bronchoscopic examinations that the bronchi become constricted during the expiratory phase of a cough. If this is true, then the efficiency of the expiratory blast in carrying away secretion is further enhanced. The principle would be much the same as that involved in the choke of a shotgun barrel. The push behind the charge of shot is more effective if the barrel is narrowed at the muzzle.

Material. The material used in this report consists of the records and pathological material from 39 fatal cases of asthma, twelve of influenza, and ten of bronchopneumonia found in the files of the pathology departments of the University of Minnesota, St. Luke's and St. Mary's Hospitals, at Duluth. The experimental animals used were rabbits.

Asthma. A review of a number of asthma cases soon convinces one that asthma is not a disease entity but merely a symptom syndrome. This group included quite a variety of diseases. Seven were omitted because they were irrelevant or because the sections were unsatisfactory. One proved to be a case of acute tracheobronchitis, which is discussed separately. The remaining 31 fall into four groups, as far as the pathology of the bronchial epithelium is concerned, as follows: (1) 12 showed the metamorphosis from ciliated cells to mucus-producing, non-ciliated cells; (2) 11 were characterized by surface destruction from bronchitis; (3) 5 exhibited the marked bronchial constriction that is usually thought to play such a large role in asthma with but little or no destruction of the epithelium; (4) 3 had pneumonia, with little or no change in the bronchial epithelium. We are concerned only with the first two groups.

Fig. 4.

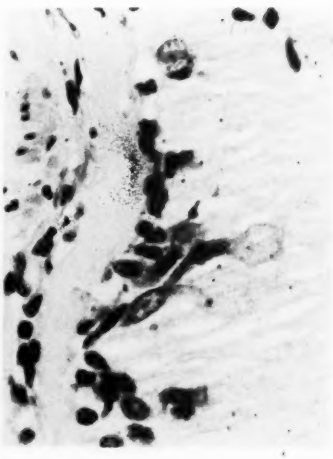


Fig. 5.

Fig. 4.—Low power photomicrograph of bronchial epithelium in a fatal case of asthma of twenty years' duration. The entire epithelium is melting into the secretion accumulated in the lumen. There are no ciliated cells whatever in this area. It can readily be understood from this illustration why the mucinous mass contained in the air passages remains in place. There are no cilia to move it. One can also see why it clings to the wall so tenaciously when attempts are made to remove it by aspiration or by means of forceps. It is, in fact, actually an integral part of the mucosa. In this illustration also, it looks as though the nuclei had been dragged away by traction from their normal positions in the epithelium.

Fig. 5.—High magnification of a field from Fig. 4.

The metamorphosis of the columnar ciliated epithelium seems to begin deeply within the individual cells with the formation of a droplet of mucin.[14] This droplet enlarges until it eventually lifts the plate of cilia from the end of the cell and escapes, and the cilia then become lost lost entirely (Figs. 1 and 2). The secreted mucin, however, does not always escape completely. It protrudes from the cell which produced it, fusing with the mucinous mass in the lumen but still remaining attached to the interior of the cell (Fig. 3). Eventually the entire cell seems to melt into or be dragged into the mucinous mass in the lumen (Figs. 4 and 5). The nucleus may be found at some little distance from the basement membrane. This change does not occur in just a few cells of the bronchial mucosa but involves most of them. In the eleven cases showing extensive metamorphosis the change involved from approximately 30 per cent to 100 per cent of the cells in the areas examined.

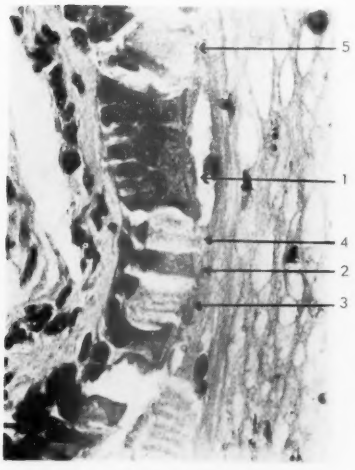


Fig. 6.—From the same case as Figs. 4 and 5. Photomicrograph of another area of bronchial epithelium. Here some ciliated cells have been preserved. The mucus in the lumen appears to be free over the cilia, but is attached to the epithelium in the secreting cells. This area suggests that the individual ciliated cells may actually become secreting cells. The different appearances of the individual cells might be different stages in the metamorphosis. Note the differences in the ciliated plate, the protoplasm, and the nuclei in the numbered cells.

There were twelve patients in the group which showed the metamorphosis. In eleven it was very extreme; in the other one, moderate. Death in eight of the twelve was due to respiratory obstruction and exhaustion. The mode of death is not mentioned in three, and in the remaining one, death was of the pneumonic type. Asthma had been present 11 years on an average—from 3 to 22 years. Unfortunately the records are incomplete as far as history of allergy and blood counts are concerned, but nine of the twelve gave a history of allergy or showed eosinophilia.

Plugging of the bronchial tree by thick mucinous secretion is described in ten. The air passages were said to be filled "with mucus and frothy material" in one of the remaining two, and, in the other, the pathologist said that the air passages were "closed by swollen mucosa". There were no other significant pathological findings in seven of the twelve, excepting those of asthma. Active tuberculosis was found in one, and signs of right heart failure in three. Broncho-

pneumonia was described grossly in two, but the sections did not show any.

It has been suggested that these findings in the epithelium might be due to postmortem change. However, I feel that postmortem change can be ruled out on the following facts: (1) Necropsy was performed on six of these patients less than four hours after death—in two less than one and a half hours after death. (2) Islands of well-preserved cilia were found in eight of the twelve. In postmortem change the cilia are lost uniformly. (3) Postmortem change in the epithelium is fairly typical. The changes found in these cases were of a different type entirely.

The effect of the metamorphosis is threefold. First, an additional amount of viscid mucin is produced. This in itself should not be serious since it is of the type which is removed most rapidly under ordinary circumstances. But, secondly, the entire ciliary mechanism is lost. What Proetz has called the "escalator" function of the mucosa is gone, the mucus accumulates until the air passages are full because there are no cilia to remove it, and to further aggravate matters for the distressed patient, the mucinous mass remains attached to the interior of myriads of epithelial cells. Actually the mass in the lumen is an integral part of the mucosa (Figs. 4, 5 and 6). At necropsy it is often difficult to detach with forceps. Steinberg[13] has pointed out that the mucus plugs are "adherent to the bronchial walls." It seems likely that this firm attachment of the secretion to the mucosa accounts for the ineffectiveness of cough in the asthmatic. The blast of air as it passes over the mucus and through the constricted channels fails to dislodge it, but exerts enough traction to stretch out some of the epithelial cells (Figs. 3, 4 and 5). At the same time the alveolar walls give way under the oft repeated increase of air pressure and emphysema develops.

Asthmatic patients ordinarily do not become asphyxiated in their first attack. They suffer through many of them. One wonders just what happens in the mucosa in these nonfatal attacks. Probably the metamorphosis is not extensive enough to cause death. The goblet cells may be sloughed out as the attack subsides, and ciliated cells may be formed again. At least we know that in the nose and sinuses the ciliated cells are lost under certain conditions and replaced very quickly. Of course bronchospasm may be a factor in many or all of these attacks.

The cause of this metamorphosis is not known. It seems to be related to allergy, since allergy, or eosinophilia, is prominent in the

history of nine of these twelve patients. This number is too small, however, to mean very much statistically. I have one section of a polyp removed from the maxillary sinus of an allergic patient that shows extensive goblet cell formation. On the other hand, one could scarcely imagine that the metamorphosis obtained behind the closed nostril in the rabbits was allergic in origin. Perhaps stoppage or reduction of air flow is the cause in both the animals and the patients, or it is possible the change in the experimental animals has no relation to that found in these patients.

If the metamorphosis is an expression of allergy, then the asthma which shows this metamorphosis is doubtless a disease entity in which the chief pathological change in this picture is in the respiratory epithelium. The other outstanding pathologic features, which are usually considered to be the significant ones, namely, excessive production of mucus, formation of mucous bronchial casts, emphysema, thickening of basement membranes, hypertrophy of muscles, dilatation of bronchioles, could be secondary to the epithelial change. The degeneration of the mucous glands is probably much the same process as that going on in the epithelium.

Asthma with Bronchitis. Altogether there were eleven cases in the second group of asthmatics. These were not all similar, but they all showed more or less destruction of the ciliated surface cells in the bronchi and bronchioles. The bronchial tree filled up with secretion, which, unlike the other group, was characterized by the many pus cells it contained. Some of these patients died of asphyxia, as in status asthmaticus, and in these, loss of the ciliary mechanism doubtless played much the same fatal role as in the first group.

The average duration of the asthmatic symptoms in this group was fifteen and a half years. There was no clear cut history of allergy in any. Differential blood counts were recorded in seven, only two of which showed any degree of eosinophilia, and in these it was not great—four per cent in one and five per cent in the other. There is a record of a considerable number of eosinophiles in the sections in only one case, and a few in one other. The absence of eosinophiles is noted in some. Seven of these patients died in severe respiratory distress, two died cardiac deaths, and in two the mode of death is not recorded. At necropsy the pathologist describes plugging of the bronchi in seven. The bronchi contained quantities of pus in three, and in one the mucosa was edematous and congested. Bronchopneumonia was found in three, bronchiectasis in two, and active tuberculosis in one.

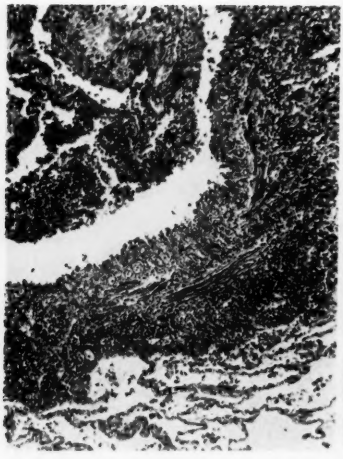


Fig. 7.

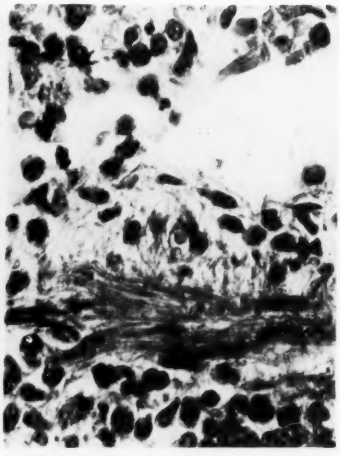


Fig. 8.

Fig. 7.—Low power photomicrograph of the bronchiolar epithelium from a fatal case of acute tracheobronchitis. There is an extensive, severe, purulent inflammation with radical changes in the epithelium. The epithelium has lost its columnar form and is exfoliating at the surface. No cilia whatever could be found in this case.

Fig. 8.—High magnification of an area from the preceding.

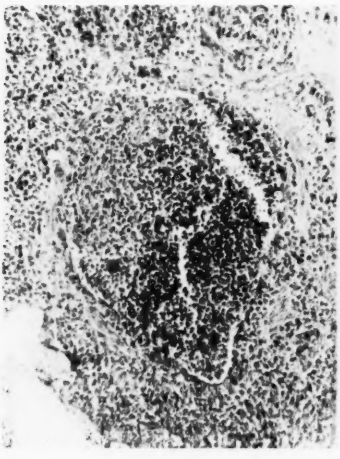


Fig. 9.

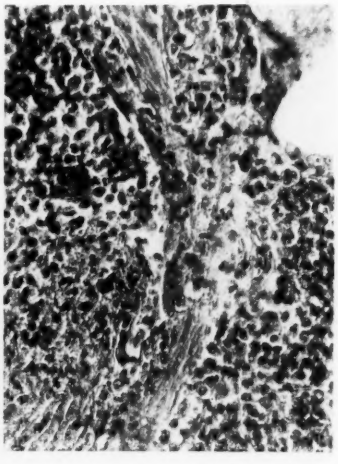


Fig. 10.

Fig. 9.—Photomicrograph of a bronchiole in a fatal case of influenza from the pandemic of 1918. The epithelium is entirely destroyed and the lumen is filled with a purulent secretion. This type of secretion can be moved up vertical surfaces by ciliary action when the ciliary mechanism is intact, but not as rapidly as the viscid, mucinous type. In this case all of the cilia were destroyed. This was doubtless a factor in the accumulation of the quantities of secretion in the air passages. How important this factor might be is unknown.

Fig. 10.—High magnification of a section of the above.

The bronchial epithelium in this group also was found to be practically devoid of cilia, but the picture was essentially different. There was no extensive change to secreting cells in any of them. (A few goblet cells were noted in two.) There was very extensive loss of the ciliated surface cells by destruction in all. The secretion was characterized by a high content of neutrophiles. In this group also, death occurred in most instances because the air passages filled up with viscid secretion. This probably could not have occurred had the ciliary mechanism been functioning.

There was one case of acute tracheobronchitis which had been classified as asthma and which deserves some special attention. This patient died of asphyxia, and at necropsy the entire bronchial tree contained thick tenacious plugs of mucus. The cut surface exuded abundant fluid, especially in the upper lobes. This man did not have asthma. He had been ill only three days with an acute illness which began with rhinitis. His first "asthmatic" symptoms appeared just the night before he died, when he developed severe dyspnea. Adrenalin gave transitory relief only. He was hospitalized and placed in an oxygen tent and again given adrenalin without any improvement. Pantopon and atropine seemed to give some immediate improvement, but he died one hour after this medication. Microscopic examination revealed that the entire bronchial and bronchiolar epithelium in the sections available had been sloughed off down to the last layer of stellate cells next to the basement membrane (Figs. 7 and 8). There was not a vestige of a cilium anywhere. The lumena were filled with purulent exudate. This patient would probably not have died of asphyxia had the ciliary mechanism been there to remove the thick secretion. Conceivably, aspirations through a tracheotomy might have saved him.

Influenza. At the university, I examined twelve cases of influenza from the files of the Department of Pathology. All of these patients perished in the pandemic of 1918. The histories indicated that the patients died deaths which were currently described as "drowning in their own secretions." These patients generally filled up with a thin, frothy secretion and died after brief illnesses. At necropsy the lungs were edematous and exuded copious quantities of watery, blood-stained fluid on section. There were only a few lung sections saved from each case, and most of these were taken near the periphery. Some bronchioles were found in each, however. The essential picture in these sections was that of an acute bronchitis with beginning pneumonia. The bronchioles were filled with exudate, and the epithelium was very badly damaged (Figs. 9 and 10). In two

cases the epithelium was destroyed to the last cell as far as could be determined. It was largely gone in seven, and in two more, partially gone. In only one case was the epithelium fairly intact, and in this one the surface cells were so generally exfoliated that only a few cilia could be found.

We have learned[15] that during the common cold there is very extensive loss of ciliated cells in the nose during the acute stage. In fact, it is so extensive that the surface seems to be all but completely denuded of cilia. Living, ciliated cells are found floating free in the secretion in untold thousands during this stage. In a day or two, as soon as the acute stage is over, the cilated cells are found to have been restored.

If this temporary loss of ciliated cells obtains throughout the bronchial tract in influenza (or any other condition) as it does in the nose during rhinitis, then it is quite conceivable that the resultant loss of ciliary action might be a potent factor in the accumulation of such quantities of fluid secretion as to drown the patient. In acute rhinitis, the copious secretion pours from the nose by gravity, but the secretion produced during acute influenza bronchitis accumulates by gravity in the lower part of the tract, unless it is lifted out by ciliary action, or is coughed out, or removed artificially. However, this very fluid secretion is the type which is moved most slowly up vertical surfaces by ciliary action. All but a thin capillary sheet slides off. Perhaps the production of secretion was so great in those influenza patients that they would have drowned even with an intact ciliary mechanism. Almost surely, however, the loss of ciliary action was a factor. How great a factor it was must remain in the field of conjecture, awaiting more study. It would seem that these cases would have been ideal for aspiration. The secretion was so liquid that it could easily have been removed. It should have been comparatively easy to tide these patients over the danger period of a few days, if the ciliated cells were as rapidly replaced as they are in the nose during the common cold.

Bronchopneumonia. The question now arises, does loss of the ciliary mechanism play a rolė in the development of pneumonia? It is not usually supposed that it does.[16]

The records of ten patients dying of bronchopneumonia were reviewed, and the microscopic sections of the lungs examined. In these sections, there were all degrees of pneumonia and all degrees of destruction of bronchial epithelium. In most of the cases, there were areas where the bronchial epithelium looked normal and other areas where it was completely destroyed. The order of events could

not be determined. I do not believe that the question can be answered from the ordinary necropsy material. A single case studied very thoroughly, taking serial blocks through the entire tract for microscopic examination, would be more apt to give the desired information.

EXPERIMENTAL WORK

If loss of ciliary action is a factor in the development of lung pathology, then destruction of ciliated epithelium in the experimental animal should produce changes below the destroyed area. I showed some instances of experimental sinusitis two years ago which had been produced by destroying the epithelium at the osteum. If the cilia are destroyed over an annular area in a bronchus, what will happen distal to that point? A number of experiments have been done on rabbits, attempting to destroy the bronchial epithelium through a bronchoscope. Several methods have been tried, most of which did not yield results. It is not easy to destroy the epithelium completely without also destroying the underlying structures as well. Fatal pneumonia, bronchiectasis, and emphysema have been produced in a few rabbits, however, by endoscopic manipulation and results look promising. Beyond that, one could not say anything at this time.

SUMMARY AND DISCUSSION

There is a group of cases among patients who die from asthma which shows a very striking and characteristic change in the bronchial epithelium. This change has been noted briefly in the literature a number of times and has been rather fully described, but it does not seem to be understood nor its importance appreciated. It is entirely ignored in the great majority of descriptions of the pathology of asthma. The change consists in the substitution of goblet or goblet-like cells for the normal columnar ciliated cells. Apparently it is a true metamorphosis. As the metamorphosis takes place, the ciliary mechanism is lost, and the characteristic viscid, mucinous secretion accumulates in the air passages. Normally, this viscid type of secretion is very readily carried up vertical surfaces by ciliary action. The amount of secretion is enhanced because the erstwhile ciliated cells are secreting as well as the glands. The difficulty of removal of the secretion is aggravated, because the mucin remains attached, over large areas, within the cells which produce it, thus anchoring the mass to the wall. When the air passages have become sufficiently filled, the patient dies of asphyxia. In my opinion, this metamorphosis is the chief pathologic change and, in my opinion, death results directly from the loss of ciliary function.

There is a second group of asthmatics in which the cilia were also lost, but the picture was essentially different. In this group, chronic bronchitis with purulent secretion was prominent. There was destruction at the surface of the bronchial epithelium, and the ciliated cells had sloughed off very extensively. In these patients, also, the air passages filled up with secretion to such an extent that the patients died. Presumably the stasis and accumulation occur largely because of loss of ciliary action.

Bronchospasm must not be forgotten. It was doubtless a factor in some of these cases. In one of the groups, which was omitted from this discussion, spasm seemed to play a dominant role.

The single patient with tracheobronchitis who was found also died in extreme respiratory distress. In this patient, the ciliated epithelium was practically entirely destroyed, and, according to the necropsy notes, all the bronchi contained viscid plugs of secretion. Presumably, this secretion could have been removed by ciliary action had the mechanism not been destroyed.

In the pandemic of influenza in 1918, many patients died in acute respiratory distress with the air passages and lungs filled with a thin, frothy, liquid secretion. The pathologic material from the lungs of twelve of these patients was reviewed. The material was not entirely satisfactory, but, as far as could be determined, the bronchiolar epithelium had been entirely destroyed and all cilia with it. This type of secretion is not removed as rapidly by ciliary action—at least against gravity—as are the more viscid types, but undoubtedly the loss of ciliary action was at least a factor in the accumulation of quantities of secretion in the air passages. How important this factor was, must remain a matter of conjecture awaiting further study.

In all of these groups, the two types of asthma, the tracheobronchitis and the influenza, I believe that mechanical removal of secretion as a substitute for ciliary action is indicated. Aspiration, either through a bronchoscope or a tracheotomy, would be the method. It has been used more or less successfully in asthma for years and more recently has saved the lives of patients ill with acute laryngo-tracheo-bronchitis and postoperative atelectasis.

A beginning has been made to study the role of loss of the ciliary function in the pneumonias. Nothing positive can be reported at this time. In a group of bronchopneumonia cases, which were reviewed, the necropsy material was found to be unsuitable. The only

way in which suitable material may be obtained would be to section the lungs specifically for the purposes of this study.

I am indebted to my associate, Dr. D. L. Tilderquist, for financial aid in making this study.

726 Medical Arts Building

REFERENCES

1. Hilding, A. C.: Experimental Surgery of the Nose and Sinuses I, Arch. Otolaryngol. 16:9-18 (July) 1932.

2. Hilding, A. C.: The Physiology of Drainage of Nasal Mucus III, Am. Jour. of Physiol. 100:664-670 (May) 1932.

3. Bell, E. T.: Text Book of Pathology, Philadelphia, Lea & Febiger, 1941, pp. 637-638.

4. Huber, H. L. and Koessler, K. K.: Pathology of Bronchial Asthma, Arch. of Int. Med. 30:689-760, 1922.

5. Marchand, F.: Beitrag zur Pathologie und Pathologischen Anatomie des Bronchial asthmas, Beitr. z. Path. Anat. u.z. allg. Path. 61:251, 1916.

6. Fraenkel, A.: Zur Pathologie des Bronchial asthma, Deutsch. Med. Wchnsch. 17:269, 1900.

7. Fowler, Kenneth: Necropsy Studies on Two Patients Dying of Asthma, Penn. Med. Jour. 40:720-724, 1937.

8. Craige, Branch, Jr.: Fatal Bronchial Asthma, Arch. of Int. Med. 67:399-410, 1941.

9. Bubert, H. M. and Warner, C. G.: Fatal Asthma, J. A. M. A. 104:1469-1472, 1935.

10. Michael, P. P. and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, Jour. of Allergy 6:150-174 (Jan.) 1935.

11. MacDonald, Ian G.: Local and Constitutional Pathology of Bronchial Asthma, Annals of Int. Med. 6:253-277 (Aug.) 1932.

12. Lamson, R. W. and Butt, E. M.: Fatal "Asthma." Clinical and Pathological Consideration of 187 Cases, J. A. M. A. 108:1843-1850 (May) 1937.

13. Steinberg, B. and Figley, K. D.: Pathology of Asthma: Nonbacterial Allergic and Bacterial Types Based on Autopsy Material, Jour. of Lab. and Clin. Med. 13:921 (July) 1928.

14. Jorgensen, J. V.: Patologisk-anatomiske undersogelser hos 3 patienter dode under asthma anfald samt et lethalt tilfaelde af "Sekretorisk asthma", Bibliotek for Laeger 128:217-266, 1936.

15. Hilding, A. C.: The Common Cold, Arch. of Otolaryngol. 12:133-150 (Aug.) 1930.

16. Blake, F. G. and Cecil, R. L.: Studies on Experimental Pneumonia, I and II, Jour. of Exp. Med. 31:403-574, 1920.

II

THE OTOSCOPIC PICTURE IN DEAFNESS*†

WERNER MUELLER, M.D.

BOSTON

The work carried on by the Winthrop Foundation for the study of deafness up to May 1, 1942, entailed the physical examination of 689 patients. This report deals with the otoscopic findings with special regard to their correlation with the histories obtained and with the results of the audiometric examinations. Since the chief purpose of the Winthrop Foundation is the study of otosclerosis, it would seem at first that emphasis on the otoscopic picture might be beside the point, for otosclerosis has always been described as that particular type of deafness in which the examination of the ear itself showed nothing abnormal. The only exception to this rule has, perhaps, been the so-called "pink blush over the promontory." Our experience during the past two years has borne out the contention of the more recent investigators of otosclerosis that normal drum findings must no longer be insisted upon. The technique used in our work did not differ from that of everyday otologic practice. Only standard ear specula and the Siegle-Bruenings otoscope were used. Apparatus affording high magnification and photography were not available.

Now, in order to appreciate the pathological ear drum properly one should have a clear idea of what a normal drum looks like, and here we are immediately confronted with a difficulty. What characterizes a "normal" ear drum? Since it is one of the peculiarities of nature that she sets no inflexible standards, we are forced to set up our own. This we do by many observations on subjects who, so far as is known, never had ear disease and who have what is regarded as normal hearing. We are dwelling on this point at some length because, for the reasons above stated, it is obvious that every otologist has his own mental image of a normal ear drum and that the evaluation of findings is at times bound to lead to disagreements among observers.

*From the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary.

†Presented before the Annual Meeting of the Massachusetts Eye and Ear Alumni Association, Nov. 18, 1942.

Pathology of the ear drum does not necessarily mean that there must be pathology elsewhere in the middle ear. On the other hand, it has been claimed that a normal drum does not always rule out significant pathology elsewhere in the middle ear. But since the middle ear cavity is very small and since the tympanic membrane forms a large portion of its wall, we are justified in assuming that a pathological drum does indicate the presence of lesions elsewhere in the middle ear and that a normal drum has a middle ear back of it that contains no lesions. The lesion that is typical for otosclerosis would be merely the exception that proved the rule. We do not wish to be dogmatic on this point of interrelationship between drum and middle ear, but we do favor the obvious over the remote.

In order to facilitate the keeping of records, each ear drum was described under definite headings and these will be dealt with in the following paragraphs in more or less outline form.

Color and Thickness. From the color of the drum inferences may be drawn as to its thickness. The normal drum color is most frequently described as "pearly grey." This appearance is due to the fact that the drum is not transparent but translucent. It will be remembered that the ear drum proper is a rather stout, fibrous membrane, covered on the inside by mucous membrane, on the outside by nothing more than skin. It contains blood vessels, lymphatics, and nerves. Although in its entirety the ear drum is very thin, its internal structure and its outer surface are such that most of the incident light can pass easily through it but is diffused as it does so, and a small portion is reflected back into the observer's eye. If it were not for this reflected light the drum would be invisible, for the eye perceives only such objects that either emit or reflect light. This concerns only partly the so-called light reflex, often misnamed the "cone of light," of which more later on. Our brief excursion into the realm of optics is necessary if we wish to appreciate the interdependence of color and thickness of the ear drum, for it is now obvious that the thicker the drum is, the less light it will transmit and the more it will reflect. In other words the thicker the drum, the brighter it will be. We all have seen drums that appeared to be as milky white as opal glass. Such drums are most certainly thicker than those which seem to consist of very thin oiled paper rather dark grey in color. If, then, in our examination we find a drum of a uniformly dark grey color, we may safely assume that its thickness also is uniform and normal.

Every inflammatory process leaves scar tissue in its wake, for it is by the laying down of new fibrous tissue that healing takes

place in all organs of the body. An ear drum, therefore, which shows evidence of regional or total thickening must have, at some time or other, been subjected to disease of some kind; i.e., if we are willing to apply to the ear the principles of general pathology. Calcareous deposits in the form of snow-white, sharply circumscribed plaques are indicators par excellence of previous severe disease. As Dr. Timothy Leary, our well-known medical examiner once said "calcium is the tombstone of dead tissue."

The lustre of the tympanic membrane can be judged only if there be a light reflex present. In itself it probably is not important because it depends merely on the state of the surface layer of the external epithelium.

The normal light reflex owes its triangular shape to the peculiar irregularly conical shape of the normal drum. It always occupies that portion of the drum surface that lies at right angles to the observer's line of vision. It must be kept in mind that this line of vision is coincident with the light rays coming from the head mirror. The curvature of the external auditory meatus or the inclination of the drum may be such, however, that none of the drum surface is placed at right angles to our line of vision. In such a case we could well have a normal drum without a light reflex. Total absence of the reflex, then, is not necessarily abnormal. The picture changes, however, if the reflex be interrupted anywhere between the umbo and the periphery, or if it should extend only along the antero-inferior periphery. Then we may conclude that the shape of the drum is not normal but in some way distorted. In general it can be stated that absence of the reflex is of no great importance, but, if present, it can give us some information about the surface configuration of the drum.

That the reflex itself enables us to note the lustre has already been stated.

Middle Ear Structures. Careful examination of the drum often reveals certain structures and landmarks of the middle ear other than the malleus, which latter deserves a special discussion. Most frequently seen is the lower end of the long crus of the incus. Next in order of discernibility are the niche of the round window and the tendon of the stapedius muscle. The region of the eustachian tube can less often be made out, and a rare treat indeed is to see the chorda tympani cross the drum behind the malleus. The visibility or invisibility of the above named structures and landmarks is valuable only in that they inform us further about the thickness of the drum. We

have observed drums that allowed us to see plainly a small blurred reflex on the promontory where the latter forms the anterior region of the niche of the round window. Some of these drums were pink over this region; others were not. We are, at this time, not prepared to discuss this feature of the otoscopic picture.

The malleus is the most prominent landmark of the ear drum. It is a badly distorted and thickened drum indeed that does not allow us to see it. Normally only the long process is visible, extending from the short process to the umbo. Its lower extremity is often gracefully curved, ending at the umbo in a scroll-like disk. Its outlines are rather sharply demarcated, giving it a rather flat appearance. The short process appears as a small prominent knob, and upward from it extend the anterior and posterior folds which outline Shrapnell's membrane. These folds are best brought out with the pneumatic otoscope. Deep retraction of Shrapnell's membrane should make the examiner suspicious of previous disease of the epitympanum.

The malleus presents two aspects which are of help in evaluating that condition of the drum that is known as retraction. These are: first, the angle which it forms with the base line of the skull; second, its lines of demarcation. Usually one varies with the other. Retraction of the malleus results in a raising of the long process toward the horizontal, a narrowing and blurring of its contour, and a greater prominence of the short process. A malleus that is retracted to an extreme degree is almost horizontal; i.e., parallel with the base of the skull, and reduced to a narrow ridge; it is also foreshortened. A so-called slight to moderate retraction does not necessarily mean anything, but marked and extreme retraction certainly does.

The tenseness of the drum and the mobility of the malleus were tested by means of the pneumatic otoscope. Since the normal limits of both are necessarily arbitrary, we regarded only marked flaccidity of the drum and marked stiffness of the malleus as significant of disease. The pneumatic otoscope often also reveals adhesion of the drum to the promontory, a pathological picture the significance of which need hardly be emphasized.

We shall now briefly state how the otoscopic findings were utilized in the Winthrop studies.

The otoscopic examination formed only a part of the work-up of each case, as has been stated elsewhere. Now, it was found very frequently that evident pathology and deafness were not at all pro-

portional, but by correlating the otoscopic findings with the history and the hearing test we have been able to group our cases for further study. Up to the first of May, 1942, 689 cases had been studied. Two hundred and ninety-nine of these, ranging from school age to adult life, were considered to be cases of straight conduction deafness. One hundred and forty-four of these showed no relevant middle ear pathology, i.e., pathology which had any possible bearing on the patient's deafness. One hundred and fifty-five had negative histories but showed evidence of tubal or middle ear pathology. The term "relevant" pathology calls for some clarification. It was used to group such cases as the following: (1) patients with one pathological and one apparently normal ear, but with identical hearing losses in both ears; (2) patients with progressive deafness who gave a definite history of middle ear disease in early childhood but in whom the deafness did not appear until many years later.

The remaining 390 cases require study over a longer period of time in order to determine what bearing the otoscopic findings have on the deafness. They include 150 cases with only high tone losses, 75 preschool children, 95 cases which are now being studied, and 70 cases which for some reason or other have been dropped.

SUMMARY

1. A description of the otoscopic picture in health and in deafness is given.

2. The data obtained aid greatly in the classification of patients with idiopathic deafness.

3. The appearance of the ear drum may at times tell us nothing of the type or the severity of the hearing loss.

412 BEACON STREET

III

AUDIOMETRIC AND WORD TEST FINDINGS PRELIMINARY REPORT*†

RUTH P. GUILDER, M.D.

BOSTON

For the past three years we have been concerned with an investigation of the types of deafness which occur during the first three decades and which are not directly due to suppurative middle ear disease. Our main research objectives are: (1) further knowledge concerning the early onset and course of deafness due to otosclerosis, with special reference to potential and incipient deafness at the younger age levels; (2) further knowledge concerning the types of high tone deafness occurring during these same years; and (3) the relation between these several types of deafness throughout childhood and the young adult years.

The investigation is being approached in two ways: (1) by making a cross-section study of that portion of the general clinic population under thirty years of age who show hearing disabilities not directly due to suppurative middle ear disease; and (2) by selecting from that cross-section study certain groups of individuals for more intensive long-range study. These groups comprise:

1. Individuals in whom a probable diagnosis of otosclerosis has been made.

2. All the children of a selected group of otosclerotic parents.

3. Individuals with certain types of high tone impairment.

The history, the physical examination, and the hearing study are all vitally important factors in the study of each individual, and absolutely essential as a basis for classification and selection for further intensive study.

---

*Read by invitation at the annual meeting of the Massachusetts Eye and Ear Infirmary Alumni Association and the New England Otolaryngological Society, November 18, 1942.

†From the Winthrop Foundation for the Study of Deafness, Massachusetts Eye and Ear Infirmary, Boston.

In a clinic devoted to the problems of deafness, the hearing study is an essential part of the initial study from the standpoint of diagnosis, prognosis and treatment. It also constitutes an essential part of the follow-up program. The hearing study should at all times give a clear picture of the degree and type of the individual's hearing disability, particularly as it affects his hearing for speech. It should also show whether the underlying pathology or defect is in the sound-conducting or the sound-perceiving mechanism, but it will not tell how the drum looks or whether the patient has had middle ear disease or other pathology in the ears, nose or throat. The physical examination and the history must contribute those all-important parts of the picture.

The initial hearing study includes an audiometer test by air and bone conduction, the Rinne and Weber tests, and a study of the individual's hearing for speech. The latter is evaluated in two ways: (1) by phonograph attachment to the audiometer, we determine the amplification necessary in each ear for him to hear a list of fifty words correctly; (2) by voice, we study his unaided binaural hearing for different types of material.

At subsequent tests, we repeat only the audiometer test and the phonograph word test. In both these procedures, intensity is controlled so that any number of subsequent tests are comparable. Valuable data is thus obtained on changes in hearing for pure tones and words in single individuals at periodic intervals, and different types of treatment are being evaluated in this way over a period of months or years.

Table 1, showing frequency characteristics of speech.*

Fundamental Voice Tones	90 – 300 cycles
Vowels	400 – 2400 cycles
Consonants	200 – 8000 cycles

Table 2, showing amount of amplification necessary to give word test score of 90 per cent.

Hearing Loss	Amplification
20 – 40 db.	5 – 30 db.
40 – 70 db.	35 – 55 db.
70 – 80 db.	55 – 60 db.

*Based on data from Fletcher, Harvey: Speech and Hearing, 1929.

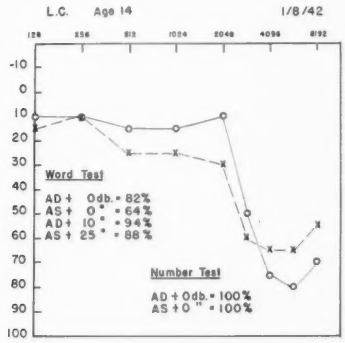


Fig. 1.—Audiogram showing high tone impairment, with reduction of word test scores, but perfect number test scores.

For the age groups studied, there is a high correlation* between hearing for pure tones and for words. When the audiogram shows a loss greater than 20 decibels at any frequency, the word test score almost invariably falls below 90 per cent. A slight drop in the lower tone range affects the hearing of the fundamental voice tones; a loss in the middle range affects the hearing of vowels and some consonants; and a loss in the upper tone range affects the hearing of consonants (Table 1). Even tone losses of over 20 decibels call for increasing amounts of amplification of the words (Table 2).

The word test has shown conclusively that impairment in the upper tone range affects the individual's hearing for consonants in the majority of instances. High tone losses often reduce the word test score, while the same individual may give 100 per cent on a number test (Fig. 1). This finding is easily explained by the fact the understanding of numbers depends largely on the differentiation of vowel sounds involving frequencies in the middle range, while the understanding of words calls for the differentiation of consonant sounds and accurate hearing in the upper tone range.

The audiogram is therefore a clear indication of the individual's ability to hear speech, and deviations in the graph at any point between 90 and 8000 cycles are usually reflected in some diminution in the individual's hearing of speech. Differences due to marked vari-

*A series of papers are in preparation giving more detailed analyses of the audiometric and word test data, and the relation between audiogram and word test scores.

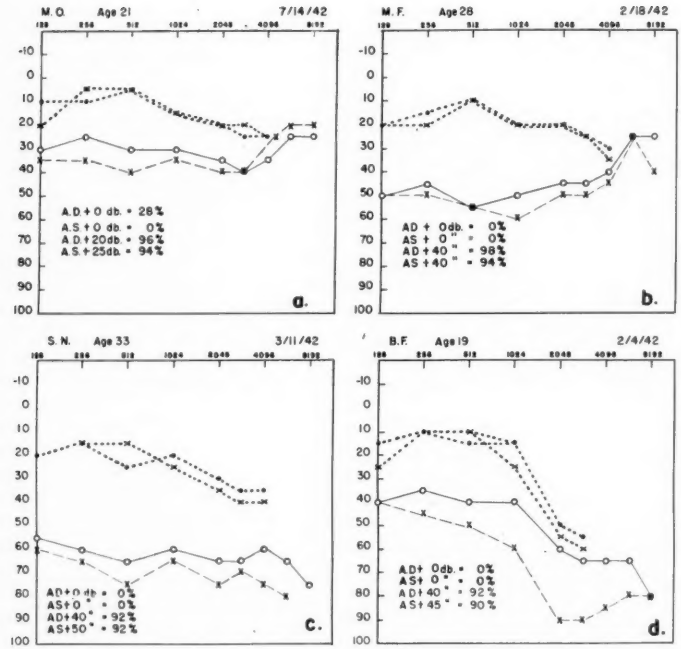


Fig. 2.—Typical audiometric and word test findings in otosclerosis group. Charts a and c show even tone losses; Chart b shows greater loss for low tones; and Chart d greater loss for high tones. Air conduction for right ear o——o; left ear x - - - - x; bone conduction for right ear .....; left ear x . . . . x.

ations in mental development or varying degrees of word deafness do not fall within the limits of this discussion. The former discrepancies between audiogram and voice test have been due in large part to a comparison of the audiogram with a spoken number test instead of with word tests given under controlled conditions.

AUDIOMETRIC AND WORD TEST FINDINGS IN PRINCIPAL STUDY GROUPS

In the Otosclerosis Group. In the otosclerosis group the audiometric and word test findings are characteristic of conduction deafness in general, and the selection of individuals has been based, as previously stated, on the combined knowledge obtained from

physical examination, history and hearing test, and corroborated in many instances by findings at operation. There are three principal types of curves which tend to recur with many slight variations (Fig. 2). In all three types there is a lowering throughout the tone range. In the first type, there is an even lowering throughout the tone range; in the second type, there is a greater loss in the low tone range; and in the third type, a greater loss in the upper tone range. There was no evidence of middle ear or tubal pathology in the four patients whose audiograms are shown in Fig. 2, and in three patients fixation of the stapes was demonstrated at operation.

The even tone impairments in otosclerosis vary from a level of 20 decibels to a level of 70 plus decibels (Fig. 2, *a* and *c*). As the air conduction curve drops, the bone conduction curve may drop for the upper frequencies, or bone conduction may remain nearly normal in the presence of a marked lowering of the air conduction curve. The duration of the deafness and the age of the individual do not seem to be the determining factors in the bone conduction changes. One patient, 42 years of age, in the parent group, whose deafness has been present for thirty years has almost normal bone conduction up to 4096 cycles, while her air conduction curve shows a marked loss. On the other hand, occasional individuals in the adolescent group, with a rapidly progressive hearing loss of only two to four years' duration, begin to show a dropping off of the bone conduction curve for frequencies above 512 cycles.

Data on the course of the hearing impairment are accumulating. Some young adults reach what seems for the moment at least to be a stationary level at 45 to 55 decibels. Long-range, continuous studies should bring to light further factors which influence the rate of progress at the different age levels. The rapidity with which a loss progresses in some of the nine to fourteen-year-olds has been astounding (Fig. 3). In spite of all the treatment which could be recommended and carried out, a considerable group have dropped some 25 to 35 decibels during two years of observation. One thirteen-year-old girl, whose older sister has a marked otosclerotic type of deafness, showed such a drop during an interval of only seven months. Two nine-year-old girls in two families with the highest incidence of otosclerosis are showing progressive losses. Some of the most marked losses, however, in the group under eighteen years of age seem very typical of otosclerosis, but present no family history of deafness.

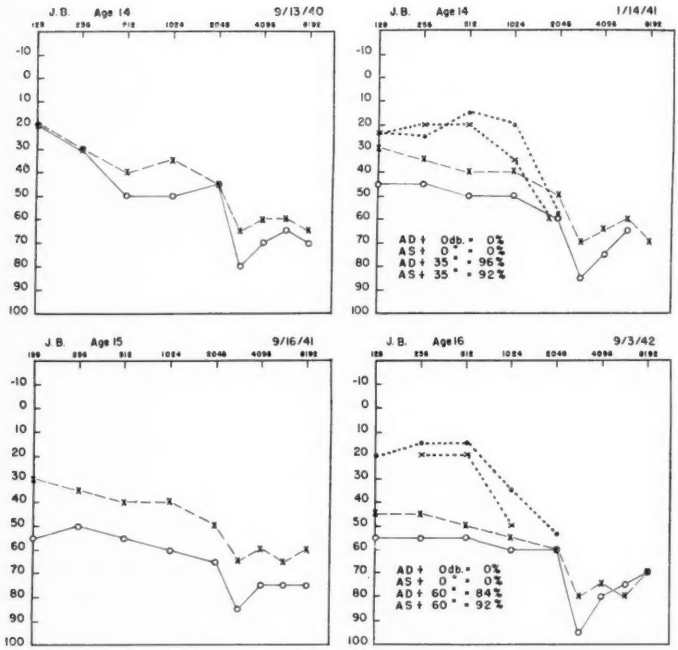


Fig. 3.—Successive audiograms showing progressive hearing loss in patient now 16, whose loss was first noticed at age of 12 years. Deafness has increased in spite of x-ray treatments of the nasopharynx.

The audiogram in otosclerosis may also take the form of an ascending curve (Fig. 2, b), with the greatest loss in the low tone range. Bone conduction may remain normal, or may show a loss for the higher frequencies. We see this ascending curve in incipient losses and in marked losses of some years' duration, so the character of the curve seems often to be preserved.

More often the audiogram shows a greater loss in the upper tone range in the otosclerotic group (Fig. 2, d). We have sufficient data to show that in some instances the first evidence of hearing impairment has been in the upper tone range, and that this range has continued to show the more marked impairment. In other instances, an even tone loss tends to show a greater impairment for high tones as the loss progresses. A change in bone conduction seems often to

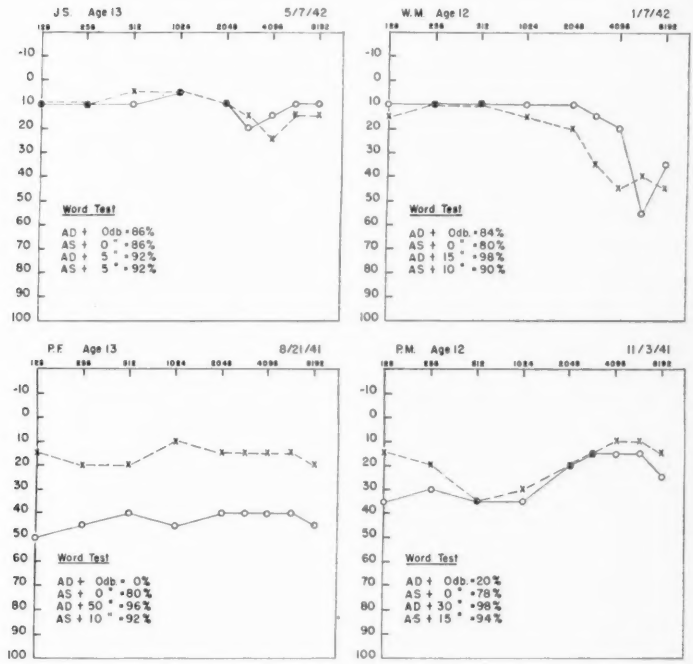


Fig. 4.—Typical audiometric and word test findings in children with otosclerotic background, showing different types of incipient changes.

precede the change in air conduction in this group. When air conduction shows a drop at 4096 cycles, bone conduction often shows a slight drop at 2048 cycles. Contrary to expectation, these changes in air and bone conduction at the higher frequencies are seen as often in the adolescent group as in the young adult and parent groups, so that this parallel change in air and bone conduction does not seem to be necessarily related to the age of the patient or the duration of the deafness. However, it is a frequent finding, as is well known, in otosclerosis of long-standing.

In Children with Otosclerotic Background. Audiograms of children with an otosclerotic background show various types and degrees of incipient hearing disability (Fig. 4). The first evidence of deviation may be a high tone drop, a general lowering of the entire curve, or a dip in the middle section. Some six-year-olds in these families are showing slight high tone drops which will be followed.

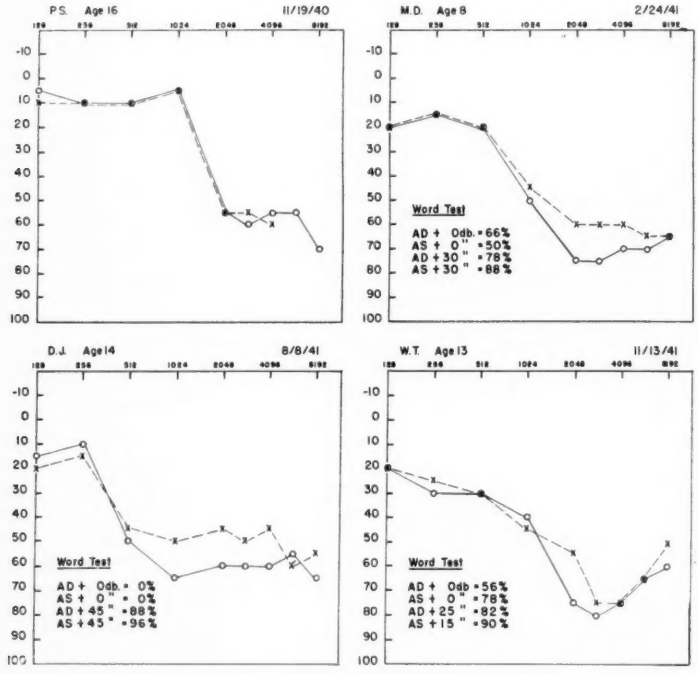


Fig. 5.—Typical audiograms in developmental high tone deafness, with drops at 1024, 512, 256 and 128 cycles.

As the study proceeds, an increasing number of children will be called for regular periodic study. All possible treatment will be carried out, and any new knowledge gained will be applied in prevention.

In High Tone Deafness. Initial studies have been carried out in a considerable number of individuals with high tone deafness. As the cumulative studies permit, they will be subdivided into groups on the basis of the underlying cause. As stated, a small group of slight high tone losses are moving over into the otosclerosis groups. A second group which is becoming clearly defined is one which we designate as developmental high tone deafness. The defect goes back to birth or infancy. Hearing is approximately normal through the lower tone range, and shows a drop at 1024, 512, 256 or 128 cycles

(Fig. 5). These individuals have normal hearing distance for the voice and some of the vowels, but often are unable to differentiate the soft high consonants beyond a few inches from the ear. They are the individuals who say, "I hear you perfectly, but I can't understand what you say." They often pass a perfect number test without amplification, but their word test score will be only 50 or 60 per cent. The majority have some residual hearing in the upper tone range. Speech development is delayed and their speech reflects the hearing defect, but they eventually proceed as essentially normal individuals.

SUMMARY

1. In a clinic devoted to the problems of deafness, such as the Winthrop Foundation Clinic at the Massachusetts Eye and Ear Infirmary, the hearing study constitutes an essential part of the initial study of the patient and of the follow-up program.

2. The initial hearing study includes pure tone audiometer tests by air and bone conduction, Rinne and Weber tests, and a study of the individual's hearing for speech by phonograph attachment to the audiometer and by unamplified voice with different types of material. Subsequent tests include only pure tone audiometer and phonograph word tests, in both of which procedures intensity is controlled; hence any number of tests are comparable. In this way, the course of deafness in individuals may be followed, and different types of treatment may be evaluated in terms of their effect on hearing.

3. Studies show that there is a high correlation between audiogram and word test score, a lowering of the hearing curve at any point resulting in a lowering of the word test score.

4. The audiometric findings are briefly discussed for the groups under special study, namely, (1) the otosclerosis group, (2) children with otosclerotic background; and (3) certain types of high tone deafness.

5. In the otosclerosis group, the audiometric findings are typical of conduction deafness in general, and the diagnosis must be based on the combined knowledge obtained from the history, the physical examination and the hearing study. The three major types of curves are illustrated and the relation between air and bone conduction discussed. The study is showing that deafness of otosclerotic origin often progresses rapidly in the 11-, 12- and 13-year-olds, and occasionally in the 9-year-olds.

6. In children with otosclerotic backgrounds, all types of slight deviation from normal hearing have been found and are being followed in the Foundation's long-range study program.

7. Types of high tone deafness occurring during the first three decades are being studied as they become defined. One group of slight high tone impairments are proving to be the incipient changes due to otosclerosis, and the curve gradually flattens into one of the typical otosclerosis curves. Developmental high tone deafness is another type which is becoming clearly defined and is being studied.

243 CHARLES STREET

IV

PENTOTHAL SODIUM IN EAR, NOSE AND THROAT SURGERY*

GEORGE J. THOMAS, M.D.

PITTSBURGH

Pentothal anesthesia is not described here with the idea of suggesting that it is a more desirable agent for ear, nose and throat surgery, nor is it claimed that it is better than other available methods. This is an age of individualization in anesthetic agents, procedures and premedications. We should not tolerate routine premedication or anesthesia for all types of patients or for all surgical procedures. The history, the physical and laboratory findings, along with the nature of the proposed operation, determine the surgical risk, the type of anesthesia and the premedication most suitable for a given patient.

Pentothal is a valuable adjunct to anesthesia and has won a definite place in the surgical field. The intravenous method of administering an anesthetic agent has a strong appeal to the experienced anesthetist, the surgeon and the patient. This method has, further, the advantage of causing a patient to traverse from the first stage to the middle of the surgical stage of anesthesia within a period of one to three minutes. Such a rapidity of action is an improvement over the ten to fifteen minute period required for inhalation anesthetics to take effect.

Among several intravenous agents studied in our hospitals, we found pentothal sodium to have the following advantages over other intravenous agents.

1. It is equally, if not more, powerful and rapid in action.
2. Twitching and jactitation are rare.
3. Postanesthetic nausea and vomiting are less frequent.
4. Relaxation appears to be more satisfactory.
5. Recovery is more rapid.

---

*Presented at the Middle Section Meeting of the American Laryngological, Rhinological and Otological Society, Detroit, Michigan, January 20, 1943.

PHARMACOLOGIC AND PHYSIOLOGIC RÉSUMÉ

A review of the more recent studies on the relationship of the barbiturates to the liver, the kidneys, and other organs reveals conflicting and confusing reports. The findings are extremely important, as they indicate that the changes produced in one species of of animal often differ from the changes in other species following the administration of the same drug.[1]

The report of our findings deals only with the human race. The findings are as follows:

1. Pentothal is a powerful respiratory depressant. The amplitude rather than the rate of respiration is mainly affected. The gravity of this reaction is lessened by the concurrent reduction of sympathetic activity and oxygen demand. Actual oxygen deprivation from either apnea or obstruction, when permitted, will invariably produce cardiac, hepatic, and cerebral damage. Overdosage, either from an excessive amount of the agent or from too rapid administration, readily produces respiratory depression.[2]

2. Laryngospasm, sneezing, coughing, and hiccups occasionally occur either spontaneously or as the result of some stimulation. Laryngospasm will invariably cause alarming cyanosis, and if permitted to continue, will result in cardiac embarrassment. These unfavorable reactions may be prevented by the administration of atropine sulfate 30 to 60 minutes preoperatively.

3. The blood chemistry reveals a slight increase in the blood sugar, but returns to normal within four hours after the administration of pentothal.

4. There is no hemolysis or change in the blood clotting.

5. No change in the red and white blood count, in the differential, or in the hemoglobin determination is found after the administration of pentothal.

6. There is a drop in the blood pressure ranging from 8 to 40 mm. The amount of the drop depends upon the rapidity of administration and the amount of drug administered. The more rapid the administration and the more used, the greater is the fall. The hypotension parallels the depth of narcosis and is probably caused by reduced sympathetic activity and oxygen deprivation. This condition should not be interpreted as one due to a toxic effect on the myocardium.

7. The pulse is usually accelerated from 8 to 30 beats per minute. This increase depends on the depth of narcosis and the oxygen want.

8. The electrocardiographic observations reveal no marked deleterious effect upon the myocardium or the conductive system of the heart, despite the findings of arrhythmia or other serious changes in animals. Occasional premature contractions may appear during deep anesthesia or during cyanosis, as in other types of anesthesia, but will disappear with a decrease in the depth of anesthesia or an increase in oxygen.[3]

9. Recent experiments definitely disprove the teachings of past years that pentothal sodium is detoxified in the liver. Despite the fact that certain authors have described anatomic changes in the liver following administration of barbiturates in animals, our clinical observations prove that the thiobarbiturates cannot be considered as specific liver poisons even after repeated use. The thiobarbiturates given by mouth may, in time, cause fatty infiltration of the liver. However, it has not been definitely proven that such a reaction occurs when these drugs are administered intravenously for anesthetic purposes.[1] Furthermore, our investigations in the human body show that the metabolic activity of the liver does not appear to be impaired by the administration of barbiturates.

10. The normal kidney is not affected, nor is any existing functional deficiency aggravated by pentothal sodium. Since the elimination of pentothal is not primarily a function of the kidney, one may, therefore, assume that even advanced renal inefficiency is not a contraindication to the use of this agent.

RANGE OF USEFULNESS

Pentothal sodium has a wide range of usefulness in surgery and medicine, such as:

1. A general anesthesia. It is an ideal agent for surgery of the mastoids, the sinuses, the nasal septum, and the larynx.

2. A rapid and pleasant induction preliminary to ether or gas anesthesia.

3. A supplement to local or spinal analgesia.[4]

4. A combatant to any toxic effect of a local anesthetic.

5. An agent which relieves convulsive states which occur with drug poisoning, tetanus, eclampsia or ether anesthesia.

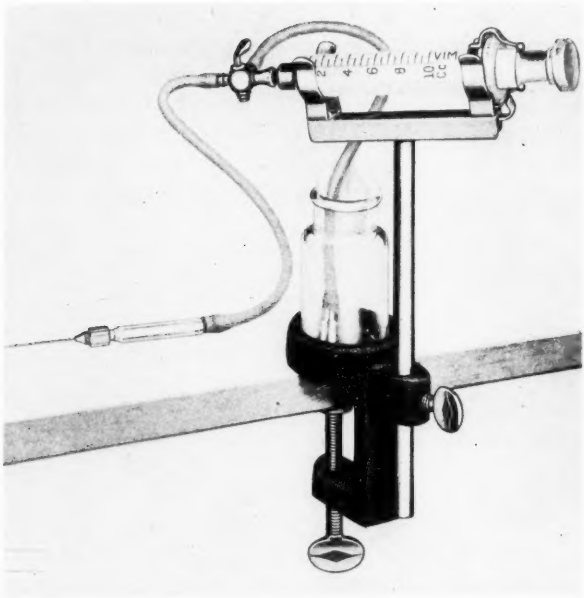


Fig. 1.—Thomas intravenous apparatus No. 2, used in the intermittent technic of administering pentothal sodium.

Pentothal sodium may be administered rectally or intravenously. Rectal administration is ideal for inducing unconsciousness and averting psychic shock while transferring the patient from his bed to the operating room. However, the intravenous method is the most practical.

TECHNIC OF ADMINISTRATION

Preoperative Medication. Sufficient and proper preoperative medication is absolutely essential for a smooth pentothal anesthesia. Opiates are used, with special emphasis placed on the necessity for atropine. These preoperative agents control the parasympathetic hyperactivity and inhibit salivary and mucous secretions, thereby greatly reducing the incidence of complications, such as coughing, sneezing, and laryngospasm. The preoperative medication should be administered hypodermically 30 to 45 minutes before the anesthestic.

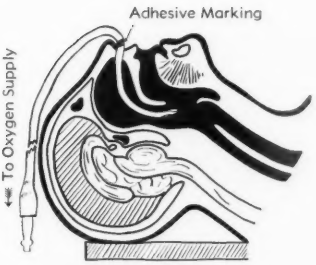


Fig. 2.

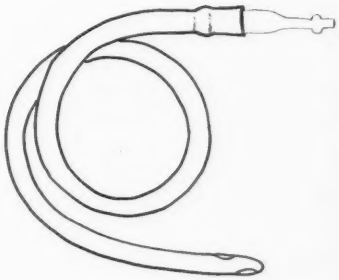


Fig. 3.

Fig. 2.—The 22 French gauge whistle-tip catheter inserted into the pharynx

Fig. 3.—22 French gauge whistle-tip catheter.

Administration of Pentothal. The dose cannot be accurately judged by the patient's weight, age, sex, or metabolic state. The dose must be adjusted to each individual patient. In order to obtain the proper depth of narcosis for the particular type of operation, one must resort to the intermittent technic in the administration of this agent. In our institutions this technic is made possible with the use of an inexpensive apparatus. This consists of a small stand that can be clamped on an arm board. The base supports a reservoir for the pentothal solution, and an adjustable bracket attached to the stand holds a syringe. A two-way stopcock is attached to the syringe, to each outlet of which is connected ordinary Dakin tubing eight inches in length. One tube leads to the reservoir and the other to the arm. To the latter is attached a glass observation tube and a needle (Fig. 1). Such equipment makes it possible to refill the syringe when necessary and to continue the intermittent technic indefinitely.

The operating field is prepared and draped. Veni-puncture is performed after the skin has been surgically prepared. Three cc. of a four per cent solution of pentothal sodium is injected during a period of 10 to 15 seconds. Because relaxation comes on more slowly than unconsciousness, it is very important that a pause of 7 seconds follow the injection of each 2 or 3 cc. of the agent. An additional 2 or 3 cc. is injected at the same rate as in the beginning, then another pause. This procedure is continued until the desired relaxation is obtained. The air passage must be patent. Oxygen must be administered with a gas machine or with a nasal adaptor, or a 22 French

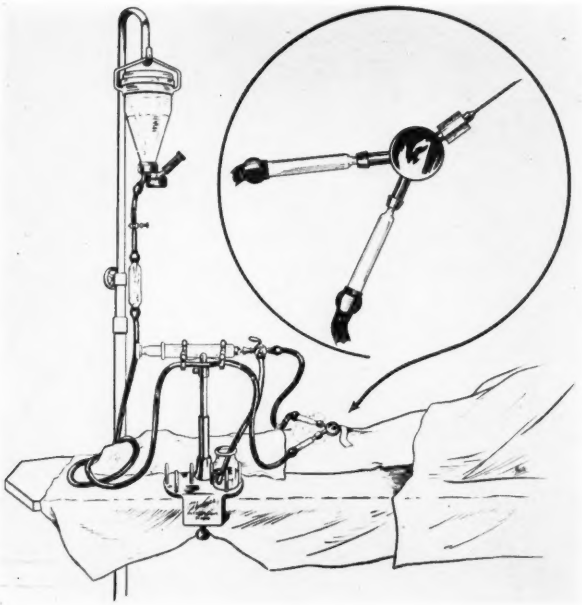


Fig. 4.—"Double set-up" apparatus for administering the supplemental solution and pentothal.

gauge whistle-tip rubber catheter inserted to a distance of five inches through the nose and into the pharynx (Figs. 2 and 3).

It must be remembered that, since the agent is given intermittently, the effect following the administration of each successive dose is increased. The pause between injections is highly important because the accumulated effect of the drug may come on very suddenly. Evidence of recovery is an indication that an additional 1 to 2 cc. of the solution is necessary. Caution regarding the speed of injection cannot be overemphasized. As in all types of anesthesia, the body has no active mechanism of defense against overdosage. The operating room is no place to demonstrate the miraculous speed of induction with this potent agent. A sacrifice of a little time will increase the safety factor in anesthesia.

Intravenous anesthesia should never be started unless there is available oxygen, either alone or on a gas machine.

In surgery requiring more than 30 minutes we have successfully used the so-called "double set-up" (Fig. 4). The supplemental solution, either glucose or normal saline, is given continuously, while the pentothal is administered intermittently when needed. This has been made possible by the use of a "manifold." The supplemental solution passes continuously through one limb of the manifold and the pentothal through the opposite limb. The male adaptor of the manifold is attached to an intravenous needle. The supplemental solution flushes the needle, thereby preventing coagulation of the blood. The supplemental solution is desirable as a stimulant and a restorative agent. This makes it possible to administer intravenous anesthesia in prolonged surgical procedures.

Special Technic for the Administration of Pentothal for Bronchoscopies, Esophagoscopies, Throat and Laryngeal Surgery. Laryngeal irritability is increased under pentothal anesthesia. Coughing or vicious laryngospasm may occur either in deep or light anesthesia. These may cause alarming cyanosis and cardiac embarrassment, if persistent. Prophylactically, we find that the administration of opiates and atropine in proper amounts will frequently control these complications. Immediately upon arrival at the operating room and before starting the anesthetic, the following procedures are carried out:

1. We apply, with an applicator, either two per cent pontocaine or four per cent cocaine to each pyriform sinus. This treatment is repeated once. The applicator is held to the pyriform sinus from one-half to one minute each time.

2. The first step is followed by intratracheal instillation of 6 cc. of one per cent larocaine. This is done with the laryngeal mirror as a guide. The patient holds the tongue forward with his index finger and thumb.*

After steps one and two have been completed, pentothal sodium is given in the usual manner.

COMPLICATIONS AND THEIR MANAGEMENT

Complications with pentothal anesthesia are rare. However, some occur and should be handled without serious results. The most common is respiratory depression. As previously stated, the amplitude of the respiration rather than the rate is affected. We found

*This technic is advocated by Carson S. Demling, Allegheny General Hospital, Pittsburgh, Pa.

that oxygen administered through a mask or a catheter is frequently sufficient to stimulate the respiration. However, occasionally we find it necessary to administer nitrous oxide and oxygen, in the meantime reducing the amount of pentothal. This technic has become quite popular with our staff.

Other complications are coughing, laryngospasm, and hiccups, which may occur either in deep or light anesthesia. These may cause alarming cyanosis and perhaps cardiac embarrassment, if persistent. Such complications are undoubtedly due to parasympathetic hyperactivity. Should they occur under anesthesia, we aspirate the mucus or other material in the pharynx, deepen the anesthesia, and immediately administer nitrous-oxide-oxygen under pressure.

Trismus is another complication. This is undoubtedly a result of parasympathetic hyperactivity that can be controlled with atropine. Should this occur during anesthesia, a nasopharyngeal tube should be immediately inserted and oxygen administered under pressure. Delay in this procedure may become serious.

Sneezing usually occurs in eye surgery. When the eye is prepared, the cleansing solution passes through the nasolacrimal duct, irritating the delicate nerve ending of the nasal mucosa and resulting in sneezing. This must be treated preoperatively. We instill two drops of two per cent pontocaine or four per cent cocaine in each eye 30 minutes before operation, again 10 minutes before operation, and immediately before starting the anesthetic.

Urticarial rash has appeared on three occasions in our series of cases. It occurred during the induction of the anesthetic and is an interpretation of idiosyncrasy of the patient to that drug. If nembutal is given the night before operation, the patient will reveal this susceptibility and this type of anesthetic can be avoided. However, should the condition occur during anesthesia, discontinue the pentothal and immediately administer four to six minims of neosynephrine intramuscularly. The anesthetic should then be continued with inhalation agents, preferably nitrous oxide or cyclopropane.

POSTANESTHETIC COMPLICATIONS AND THEIR MANAGEMENT

The most common postanesthetic complication is respiratory depression. For this reason, all patients anesthetized with pentothal should have oxygen administered to them continuously after the operation until they have completely reacted. Furthermore, the entire nursing staff of all hospitals should be thoroughly trained in the proper management of patients receiving barbiturates. The

nursing staff should be made to realize that the postoperative and postanesthetic care of patients is very important for uneventful recovery.

Postanesthetic opiates should be withheld, especially in the case of older patients, until the patient has completely reacted from the anesthetic.

If a patient has not reacted within two or three hours, it means that a toxic dose of pentothal has been administered, and the patient should be treated accordingly; that is:

1. Keep the patient warm.

2. Administer oxygen continuously.

3. Aspirate the mucus from the throat frequently.

4. Give 1 cc. of picrotoxin intravenously every 20 minutes until a slight twitching of the facial muscles is noted. Then give 1 cc. of picrotoxin intramuscularly every three hours until the patient reacts. (Extreme caution cannot be overemphasized in the use of this analeptic, since severe convulsions are invariably the result of an overdosage.)

5. Give sucrose intravenously for diuresis and dehydration of the brain and the lungs.

CONTRAINDICATIONS

Pentothal sodium should not be employed or recommended when there is a marked physiologic or mechanical interference with the respiratory function. It is contraindicated in inflammatory conditions of the neck complicated by edema of the glottis, and in tumors of the neck encroaching upon the glottis and interfering with respiration. Children under seven or eight years of age, unless very robust, are poor subjects. Apart from their natural fear and their small veins, the inertia of the air in their narrow air passages hinders gaseous exchanges and creates an undesirable situation in view of their relatively high oxygen requirements. It is inadvisable to use this agent on patients suffering with respiratory embarrassment due to cardiac decompensation. I feel that it is contraindicated in the presence of bronchiectasis, severe anemia and shock.

I also believe that pentothal is contraindicated in abdominal surgery when deep relaxation is important. Furthermore, patients suffering with intestinal obstruction react poorly with pentothal

sodium alone. In this type of surgery pentothal should be supplemented with block or spinal analgesia.

CONCLUSIONS

I have attempted to give a brief review of pentothal sodium with special attention to the pharmacologic and physiologic effects, the range of usefulness, the technic of administration, the complications and their management, the contraindications, and certain cautions as to use. I wish to emphasize that pentothal is not a drug with which liberties may be taken. Special care should be exercised in maintaining an efficient airway at all times. A gas machine should always be on hand and ready for use should respiratory depression or other complications present themselves. Finally, the drug should be administered by a thoroughly trained anesthetist who is competent to deal with any situation that may occur during the administration of this popular but potent agent.

4066 Penn Avenue

REFERENCES

1. Kohn-Richards, Richard: The Barbiturates and the Liver, Anesth. & Analg. 20:64-77 (Mar.), 1941.

2. Gruhzit, O. M., Dox, A. W., Rowe, L. W., and Dopp, M. D.: A Pharmacologic Study of Certain Thiobarbiturates, J. Pharmacol. & Exper. Therap. 60:125 (June), 1937.

3. Thomas, George J.: Clinical and Laboratory Observations on Intravenous Anesthesia, Anesth. and Analg. 17:163-168 (May), 1938.

4. Thomas, George J.: Report on 10,000 Pentothal Sodium Anesthetics, Penn. Med. J. (Feb.) 1942.

V

THE TREATMENT OF MÉNIÈRE'S SYNDROME WITH MAGNESIUM SALTS

ALFRED SCHICK, M.D.

NEW YORK

The term, Ménière's syndrome, is applied to certain symptoms and signs which occur in seizures. They consist of the appearance of vertigo, tinnitus, diminution of hearing, rotatory nystagmus, pallor, nausea, vomiting, headache, occasionally visual disturbances, and even unconsciousness. Any one of these manifestations may represent a more or less prominent and severe feature in the attacks. One symptom may also precede the others by months and years or the complete picture may set in at once.

Only the acute spells are characteristic of Ménière's syndrome, but quite often there are deviations from the normal during the intervals. Tinnitus and dizziness of varying degree may be present between the fits, and in chronic cases hearing becomes increasingly impaired in the course of time.

This syndrome can be merely symptomatic. In such cases it may be one of the clinical manifestations of an underlying disease, e.g., syphilitic neurolabyrinthitis, otosclerosis, chronic adhesive process of the middle ear, Paget's disease, arteriosclerosis of the brain, leukemia. But there remain a number of cases in which no tangible etiology can be found at all. For these forms the names "Ménière's disease"[10 19] or "idiopathic Ménière's syndrome"[4] have been suggested to differentiate them from "symptomatic Ménière's syndrome."

Although we must concede that we are far from fully understanding the idiopathic Ménière's syndrome, we have to mention the various attempts to explain the basic physiopathologic mechanism. Furstenberg[11] has found an abnormal retention of sodium by the body. He concluded that the symptoms of the syndrome were due to an increased avidity for, or an unusual sensitivity to, sodium, of the local tissues involved. Mygind and Dederding[18] assume vasomotor disturbances as a causative factor leading to a retention of water generally as well as in the inner ear. They observed accumulation of water during the periods of attacks, but do not mention

any variation of water metabolism in the single seizure. Thus Mygind and Dederding's observations seem to indicate a certain parallelism between water retention and increased tendency to seizures of Ménière's syndrome. On the other hand, the condition was improved when a large amount of water was eliminated by profuse perspiration or polyuria. Brunner[3] also holds the vasomotor disturbances producing exudation of plasma and cells in the inner ear responsible for the clinical picture of some cases of idiopathic Ménière's syndrome. He calls this kind of serous exudation "otitis vasomotorica interna." Clinically, the important role of the vasomotor system is indicated, too, by the intermittent character of the disease, the relatively short duration of the seizures and the simultaneous occurrence of other vasomotor conditions in the same individual, such as migraine, angioneurotic edema, and vasomotor rhinitis. These combinations are described by Escat,[25] Matzdorf,[26] Brunner and Spiegel,[6] Mygind and Dederding.[17, 18, 19]

The treatment of symptomatic Ménière's syndrome should be aimed, if possible, at the primary disease. For the cure of the idiopathic syndrome a confusing number of radical and conservative methods have been recommended. The variety of the remedies applied indicates in itself their relative inefficiency. Bromides, luminal, quinine, pilocarpine, atropine, adrenalin, ovarian extracts, galvanization, removal of foci, short wave therapy and spinal puncture are in use. Brunner obtained good results with the combination of iodine and calcium. Equally satisfactory therapeutic results have been achieved by Mygind and Dederding,[19] Furstenberg, Lashmet and Lathrop,[11] and M. Brown[2] by dietary methods. Mygind and Dederding restrict the fluid intake to combat the alleged water retention. The diet of Furstenberg includes the careful selection of food, low salt intake, and the administration of ammonium chloride to increase the excretion of sodium.

John Talbot and M. Brown[22] concluded, from their investigations, that neither water retention nor an increased sodium level in the blood are necessarily found in Ménière's syndrome. They observed clinical improvement by treating with a high potassium intake and permitting an otherwise normal diet. Atkinson[1] thinks that the Ménière syndrome is a result of a vasomotor disturbance and uses histamine or nicotinic acid and thiamin hydrochloride in his treatment.

The most successful surgical treatment is considered to be the total or subtotal section of the acoustic nerve.[10, 12, 14] Walsh and

Adson[24] value the section of the vestibular portion of the acoustic nerve as an effective measure, but advocate its employment only after medical treatment has proved itself ineffective. Some authors contend that the results of surgical interference are not convincingly superior to the harmless conservative procedures mentioned. There are cases reported in which, in spite of the section of the auditory nerve, the symptoms still persisted for years.

In view of the apparent importance of the vasomotor disturbances common to migraine and Ménière's syndrome, we consider it justified to try a form of treatment which has evidenced definite value in our experience with migraine. This consists in a series of intravenous injections of a magnesium salt solution.

Magnesium salts given parenterally have a diuretic effect. Besides they exert an influence on the entire central and peripheral nervous systems. According to the investigations of Meltzer and Auer[16, 17] the dominant action of magnesium sulphate on the body consists of depression and inhibition. This drug causes motor and sensory depression and interrupts the path of the nerve to the muscle in a way similar to curare. On account of their depressant action magnesium salts have been used as an antispasmodic in the treatment of such conditions as claudicatio intermittens and angina pectoris by Pines and Kieff.[21] Their ideas induced Lumière and Meyer[13] to employ magnesium salts in migraine-like complaints. Our experience with magnesium salts in the treatment of typical migraine cases refractory to all other methods of therapy was very encouraging.

Thus considering the importance of the vasomotor disturbances in Ménière's syndrome, we applied magnesium sulphate in this disease. We had the opportunity of treating 18 cases of Ménière's syndrome, many of them with Dr. Julius Bauer, some with Dr. Martin Buchband. Nearly all of these patients suffered from idiopathic Ménière's syndrome. Only a few of the symptomatic type caused by arteriosclerosis were included. All had previously been treated by different conservative means without any success. Our treatment consisted in intravenous injections of 5 cc. of a 50% magnesium sulphate solution. The injections were given two or three times a week, from 10 to 20 injections altogether, depending on the response of the individual patient and the severity of the symptom-complex. Sometimes the treatment was repeated after a few months. The injection had to be administered at an *extremely* low rate with the patient in the recumbent position in order to decrease the sensation of heat which arose. Observing these precautions, we never noticed any discomfort.

In many instances the success was striking. The appearance of the effects of the treatment is commonly gradual. First the giddiness outlasting the spells disappears; then the single attack becomes less intense, lacking one symptom or another of the complex previously experienced. Later on, in favorable cases, the seizures disappear completely or grow milder and less frequent. In some patients suffering from persistent tinnitus and a decreasing power of hearing, even these symptoms show improvement. (The tentative administering of magnesium sulphate in a few cases of arteriosclerotic vertigo without Ménière's syndrome seemed to influence some of them favorably.) Among the 18 patients with Ménière's syndrome the results were as follows:

In 7 cases no spells occurred during a control period of 14 months.

In 7 cases marked improvement occurred (attacks less frequent and milder; no more giddiness in the intervening periods; tinnitus less, hearing better).

In 4 cases there was no change.

Two typical cases are reported.

CASE 1.—Mrs. A. R., 50 years old, had been suffering from attacks of severe vertigo, nausea and vomiting for the past 14 years. There had been constant tinnitus and deafness during the past few years. During the previous months, the spells occurred daily. The patient had been treated previously with all possible conservative methods without any effect. The eyes were normal; the ears, otoscopically negative. There was great impairment of hearing, typical bilateral cochlear involvement, spontaneous nystagmus. In the caloric tests the period of latency was decreased on both sides; the duration was normal. The nose and the throat were negative. The Wassermann test, the urine analysis and blood findings, the x-ray of the skull, the lumbar puncture, were all negative. The blood pressure was 150/80.

The patient was given 5 cc. of 50% solution of magnesium sulphate intravenously. After 15 injections she was free from attacks and remained so for 14 months. Hearing and tinnitus in the intervening periods could not be influenced; she was able to do her housework again. After 14 months, when the attacks recurred, the injections were repeated and again a period free from spells followed.

CASE 2.—Mrs. B. D., 70 years old, had complained of paroxysmal vertigo, nausea, headache, vomiting and tinnitus for the past two years. During the recent months the dizziness became persistent. The ear drums were pale; the hearing fairly good. There was some slight cochlear involvement, and spontaneous rotatory nystagmus. The Wassermann test and blood findings were negative. There were traces of albumin in the urine. The blood pressure was 210/115; there was generalized arteriosclerosis.

Different conservative forms of treatment were completely without effect. After 10 injections of magnesium sulphate the attacks which used to occur on an

average of three times weekly appeared at intervals of months only. The spells were shorter and of considerably milder character. The vertigo in the intervening periods disappeared and the tinnitus decreased markedly.

One must admit that the theoretical basis of the magnesium sulphate treatment of Ménière's syndrome has not yet been completely established. For the time being one has to confine himself to the assumption that two factors are probably playing a decisive role. One is the recognized effect on the central and peripheral nervous system, influencing the entire vasomotor system especially in the vestibular apparatus. The other factor may be the diuretic action of magnesium salts counteracting either the tendency to sodium and water retention or exudation into the labyrinthine spaces caused by the vasomotor disorders.

Summing up the merits of the different therapeutic measures we must point out that intracranial operations are not without danger. Although fatal cases are reported rarely, even the rare occurrence must be emphasized in connection with a disease which is not fatal in itself. Besides, the operative injury of the cochlear nerve deprives the patient of his hearing and postoperative facial paralysis has been observed occasionally. These facts materially limit the indication for surgical intervention. .

The use of the common conservative methods may improve the condition of some patients, but there are always other cases which prove to be intractable. In addition, certain conservative methods, such as dietary measures, are difficult to carry out. Considering the unsatisfactory results of the familiar methods in the treatment of Ménière's syndrome, we think the report of our experience with magnesium sulphate justified. Although the number of cases treated is small and the time of observation short, it seems, nevertheless, advisable to call attention to the treatment.

10 East 85th Street

REFERENCES

1. Atkinson, M.: Etiology and Treatment of Ménière's Syndrome, J. A. M. A. 116:1753 (April) 1941.

2. Brown, M. R.: The Medical Treatment of Mèniére's Syndrome, J. A. M. A. 108:1158, 1937.

3. Brunner, Hans: Die Pathologie and Therapie der vasomotorischen Erkrankungen des Innenohres, Wien. klin. Wchnschr., 1925.

4. Brunner, Hans: Ménière's Syndrome, The Laryngoscope 10:877 (Oct.) 1939.

5. Brunner, Hans, and Grabscheid, E.: Zur Kenntnis der otitis deformans (Paget) der Schädelbasis, Virchow Archiv. 298:195, 1936.

6. Brunner, Hans, and Spiegel, E.: Uber Ohrmigraene, Ztschr. f. d. ges. Neurol. u. Psychiat. 70:18, 1921.

7. Cawthorne, T., and Fawcett, M. N.: Fluid Balance in Ménière's Disease, Lancet 2:1404, 1938.

8. Crowe, S. J.: Ménière's Disease, Medicine 17:1 (Feb.), 1938.

9. Dandy, W. E.: Ménière's Disease, Amer. Jour. Surg. 20:693, 1933.

10. Dandy, W. E.: Mèniére's Disease: Its Diagnosis and Treatment, Arch. Surg. 16:1127-1152, 1928.

11. Furstenberg, A. C., Lashmet, F. H., and Lathrop, F.: Ménière's Symptom-Complex, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, 43:1035, 1934.

12. Frazier, C. M.: Intracranial Division of the Auditory Nerve for Persistent Tinnitus, J. A. M. A. 61:327, 1913.

13. Lumière, A. and Meyer, P.: Les injections magnesiques contre la migraine, C.r.Soc. Biol. 534, 1934.

14. McKenzie, K. C.: Intracranial Division of the Vestibular Part of the Auditory Nerve for Ménière's Disease, Canad. M. A. J. 34:369, 1936.

15. Meltzer, S. J.: The Influence of Diuresis Upon the Toxic Dose of Magnesium Salts, Proc. Soc. Exp. Biol. and Med. 4:154, 1907.

16. Meltzer, S. J. and Auer, J.: Combined Action of Magnesium and Ether, Proc. Soc. Exp. Biol. and Med. 10:159, 1913.

17. Meltzer, S. J. and Auer, J.: Physiological and Pharmacological Studies of Magnesium Salts, Am. J. Physiol. 14-16:106, 1905.

18. Mygind, S. H., and Dederding, Dida: Clinical Experiments with Reference to the Influence of the Water Metabolism on the Ear, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, 47:360, 1938.

19. Mygind, S. H., and Dederding, Dida: The Diagnosis and Treatment of Ménière's Disease, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, 47:768, 1938.

20. Mygind, S. H., and Dederding, Dida: The Pathogenesis of Ménière's Disease and of Kindred Conditions in the Ear and the Rest of the Body, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, 47:938, 1938.

21. Pines, N. and Kieff, M. B.: The Treatment of Angiospasm with Magnesium Sulfate, Lancet 1:577, 1933.

22. Talbot, J. H., Brown, M. R., Coombs, F., and Consolazio, W.: Electrolyte Balance of the Blood in Ménière's Disease, Proc. Soc. Exper. Biol. and Med. 38:421, 1938.

23. Talbot, J. H., and Brown, M. R.: Ménière's Syndrome, J. A. M. A. 114:125, 1940.

24. Walsh, M., and Adson, A.: Ménière's Syndrome, J. A. M. A. 114:130, 1940.

25. Escat, E.: De la migraine otique, VII, Congress internat. d'ologie 7:244, 1904.

26. Matzdorf, P.: Beziehungen zwischen migraenosem und epileptischem Formenkreise, Ztschr. f. d. ges. Neurol. 156:574, 1936.

VI

HISTOLOGICAL FINDINGS IN MÉNIÈRE'S SYMPTOM COMPLEX*

FRANZ ALTMANN, M.D.

AND

EDMUND P. FOWLER, JR., M.D.

NEW YORK

Ménière's syndrome or symptom complex is characterized by attacks of dizziness of the peripheral vestibular type, reduced hearing and, in most instances, tinnitus. The drums are normal or show adhesive changes. Almost all the authors agree that the syndrome is caused by a disturbance of the inner ear. The syndrome occurs in various diseases, such as leukemia and syphilitic neurolabyrinthitis. In these instances, it is brought about by the same cause as the other symptoms of the underlying disease.

Repeated attacks are observed, however, in many individuals in whom no definite disease appears to be present. The intervals between attacks are of various lengths and during these periods the vestibular symptoms usually disappear completely and only the reduced hearing and, frequently, the tinnitus persist. In some cases only one ear is affected; in others both. The affection lasts for many years, sometimes throughout life. The dizzy spells disappear eventually in many instances but the hearing loss is progressive and may lead to complete deafness. The tinnitus persists frequently for a very long time. These cases present a characteristic clinical picture and have been called "idiopathic" or cases of Ménière's "disease," or better "Ménière's symptom complex." Many authors object to "disease" because the term indicates that these cases are a pathogenetic entity, an assumption for which the proof is still lacking.

Autopsy reports of cases of Ménière's symptom complex were extremely scarce until recently. The findings were inconclusive and did not contribute to the solution of the pathogenesis of the condition. Since 1938 the histological findings in ten cases have

*From the Department of Otolaryngology, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital in the City of New York.

been reported in which a considerable dilatation of certain parts of the endolymphatic system was the outstanding pathological change.[18, 35, 19, 30, 24] In six of them Ménière's syndrome had been present during life, in three only deafness is mentioned in the clinical records, in one no history was available. According to Lindsay,[21] it is well conceivable that in these cases also the full syndrome was present at an earlier stage of the disease, but that it was not mentioned in the records. The attacks of dizziness disappear sometimes after a few years, whereas the deafness progresses. The dizziness might have been mistaken for a manifestation of gastrointestinal disturbances and not been mentioned in connection with the ear symptoms.

The number of histologically examined cases and particularly of those with a complete clinical history is as yet too small to permit definite conclusions. Under these circumstances it seems worth while to report three new observations.

REPORT OF CASES

CASE 1.—H. P., 54 years old, was admitted Feb. 3, 1941. Sixteen years ago the patient began to have mild attacks of dizziness. Two years after the onset, he had a severe seizure which lasted about five hours. Since that time, he had had similar attacks, associated with nausea and vomiting, at two to five month intervals. During the last four months the attacks occurred more frequently, in the last weeks every day. About 12 years ago he began to notice a buzzing noise in the right ear. Frequently he could predict an attack by the change in pitch and volume of the tinnitus. About ten years ago a slowly but steadily increasing deafness developed in the right ear.

The examination showed both ear drums to be somewhat thickened. The septum was deflected to the left; the mucous membrane was pale; and the turbinates hypertrophied. No pathological changes were found in the throat, the nasopharynx, or the larynx. The audiogram for the right ear showed a loss of 56-60 db. for air conduction for all frequencies; for bone conduction only 2048 d.v. were heard (Fig. 1).

The vestibular tests were as follows:

After rotation (10 times in 20 seconds)

to the right, nystagmus of 6-8 seconds duration;

to the left, nystagmus of 6-8 seconds duration.

After calorization (water at 67° F.)

Right ear: No response after 5 minutes, face-front position; few small movements in face-up position.

Left ear: Same results as in right ear.

Both the medical and neurological examinations were negative. The blood pressure was 146/100. The Kline test was negative. Roentgenograms showed skull to be normal.

Desensitization with histamine and treatment with prostigmin were unsuccessful. On March 25, 1941, a right hemisuboccipital craniotomy was performed, and the right auditory nerve sectioned. Two days later, the patient became drowsy and lapsed into coma. The wound was re-explored and no local reaction was discovered. He expired one hour after the termination of the operation.

The autopsy showed a hemorrhage into the right cerebellar hemisphere, with rupture into the fourth ventricle, and a herniation of the cerebellar tonsils into the foramen occipitale magnum. Otherwise the brain, including the pons and the medulla, was free from pathologic changes. The vestibular and cochlear nuclei, and the fasciculus longitudinalis posterior had a normal appearance.

HISTOLOGICAL EXAMINIATION OF THE TEMPORAL BONES

(serial sections)

Right Side

External Auditory Meatus and Drum Membrane. These showed no abnormalities.

Middle Ear. The niche to the round window is filled with connective tissue of embryonic character which contains a moderate amount of fat cells. There are a few abnormal mucosal folds and bands in the anterior attic and between the anterior crus of the stapes and the promontory. Otherwise no pathological changes are found.

Mastoid. The mastoid is well pneumatized. The lumen of the antrum and of some of the adjoining cells contain a few mucosal folds and bridges of organized tissue. The pneumatic cells do not extend above or beneath the labyrinth and the petrosal tip consists of cancellous bone.

Inner Ear. The bony labyrinthine capsule does not reveal any abnormalities. The cochlear duct is extremely dilated and Reissner's membrane is pushed to the wall of the scala vestibuli. In large areas the perilymphatic space of the scala vestibuli is practically obliterated (Fig. 2). Only in a small area in the lower half of the basal cochlear turn is there a small remnant of the perilymphatic space (Fig. 3). Nowhere is there evidence of fixation of the displaced membrane of Reissner to the wall of the scala vestibuli by organized connective tissue. In many places a very thin layer of pink-staining perilymph

separates the distended membrane from the endosteum of the wall of the scala vestibuli. Through the helicotrema, the dilated cochlear duct bulges into the apical part of the scala tympani (Fig. 2). Corti's organ is reduced to a flat mound of disintegrating cells among which, in some places the external and internal pillar cells are still recognizable. The stria vascularis does not show pathological changes. Corti's organ and some other parts of the cochlear duct are covered with a thin layer of a homogenous pink-staining mass. The number of the ganglionic cells and the cochlear fibers is reduced, particularly in the basal turn, otherwise the spiral ganglion appears normal in hematoxylin-eosin specimens.

The ductus reuniens is dilated. The saccule and utricle are considerably dilated and contain some pink-staining coagula. The saccule covers the inner surface of the footplate of the stapes. The cysterna perilymphatica of the vestibule has almost disappeared (Fig. 4).

The membranous semicircular canals show normal width; only the ampullar end of the horizontal canal is slightly dilated. The border between the utricle and the semicircular canals is very sharp. The dilated utricle bulges into the proximal parts of the perilymphatic spaces of the semicircular canals, particularly into the common crus of the vertical canals (Fig. 5), the lean end of the horizontal canal and the ampullated end of the posterior vertical canal, without causing any marked distortion of the ampulla of the posterior vertical canal. Due to the herniations of the utricle into the perilymphatic spaces of the canals and the lack of changes in the membranous canals, the latter seem to protrude into the utricular lumen. The macula sacculi and utriculi show marked, the cristae ampullares only moderate, postmortal changes.

The saccular and utricular ducts are considerably dilated and appear as mere continuations of the saccule and utricle. The proximal part of the endolymphatic duct (Sinus I^3) is also slightly dilated and opens into the utricle and the saccule which communicate with each other at this place through a wide opening. The utricular fold is well preserved (Fig. 4). The intermediate dilatation (Sinus II) shows relatively few folds and complete absence of the subepithelial layer of well-vascularized areolar connective tissue which is usually found in the folds and recesses (Fig. 6). The epithelium covering the folds is flat. Many of the recesses contain pink-staining colloidlike masses. The endolymphatic sac (Sinus III) is well filled and its structure normal.

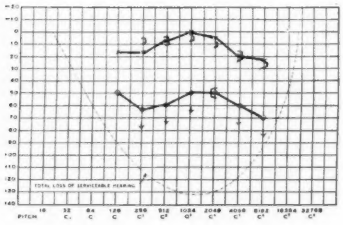


Fig. 1.—Audiogram showing hearing curve for Case 1.

The cochlear aqueduct is permeable in its entire length and contains fresh blood in some parts. There is considerable accumulation of fresh blood in the scala tympani opposite the internal opening of the aqueduct. Blood is also found on many other places in the scala tympani of the lower and middle turn.

The fundus of the internal auditory meatus contains a coagulum consisting of a network of fibrin with many red and white blood cells and cholesterol crystals. The auditory nerve is cut across approximately at the neurogliar-neurolemmal junction. There is edema and perivascular inflammatory infiltration between the bundles of nerve fibers. The cells of the vestibular ganglion appear normal.

Left Side

External Auditory Meatus and Drum Membrane. These are normal.

Middle Ear. This shows exactly the same condition as described on the other side.

Mastoid. The mastoid and the petrosum show the same condition as on the other side.

Inner Ear. The labyrinthine capsule is normal. The membranous labyrinth does not show any pathological changes. Corti's organ and all the other end-organs show the same extent of postmortal changes as on the other side. The endolymphatic duct shows in its intermediate sinus a flat, epithelial lining and relatively few folds

and recesses. Within the folds on some places a thin layer of loose areolar tissue is seen, otherwise the perisaccular tissue is fibrotic (Fig. 7). The endolymphatic sac (Sinus III) is well filled. The cochlear aqueduct is permeable and contains some fresh blood. Some blood is also found in the lower and middle turn of the scala tympani. The fundus of the internal auditory meatus contains a small amount of blood. The neural elements are normal.

SUMMARY OF THE PATHOLOGICAL CHANGES IN THE INNER EAR

Right side. There is extreme dilatation of the cochlear duct with herniation through the helicotrema; very marked dilatation of the ductus reuniens, the saccule, the utricle, the utricular and saccular ducts; herniation of the dilated utricle into the perilymphatic space of the proximal parts of the semicircular canals, slight dilatation of the proximal part of the endolymphatic duct. The dilated saccule covers the footplate of the stapes. The "perisaccular" tissue is absent. There are marked postmortem changes in the end-organs and diminution in the number of ganglionic cells and nerve fibers, particularly in the basal turn of the cochlea.

Left side. There is no dilatation of the endolymphatic system. Postmortem changes in the epithelium of the end-organs exist to the same extent as on the other side. Perisaccular fibrosis is somewhat less marked.

CASE 2.—C. D., 52 years old, was admitted Sept. 10, 1939. Two and a half years ago the patient began to experience attacks of dizziness with a feeling of clockwise rotation of objects in the field of vision, accompanied by nausea and vomiting. There was never a loss of consciousness. The attacks lasted about one hour. First, they occurred daily, later they became less frequent, and during the past year the patient had been free from attacks. At the onset of the attacks he noticed that he was becoming progressively deaf in the left ear. His wife believes that he has been partially deaf for the last five years, but the patient denies this. Tinnitus was never noticed.

For the last six months, the patient complained of pain in the sternum, in the left side of the chest and in the flanks. The pain was associated with generalized weakness and loss of weight. The patient became progressively more dyspneic.

The examination showed tenderness over the thoracic vertebrae and the costochondral junctions of the third, fourth and fifth ribs on the left. X-ray pictures of the bones were suggestive of multiple myeloma. Laboratory findings were not significant. The urine was negative for Bence-Jones protein.

Both ear drums were normal. The otological examination showed marked hearing loss for all frequencies in both ears (Fig. 8). Air conduction was greater than bone conduction (examination with tuning forks).

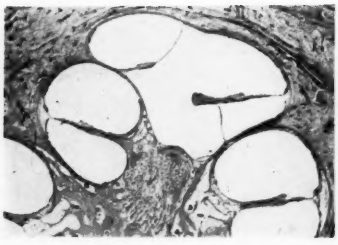


Fig. 2.

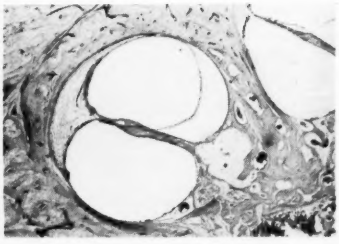


Fig. 3.

Fig. 2.—Case 1, right side. The cochlear duct is extremely dilated and fills the scala vestibuli out completely. The dilated duct is herniated through the helicotrema into the scala tympani.

Fig. 3.—Case 1, right side. Lower basal turn of the cochlea. The cochlear duct is somewhat less dilated and a small remnant of the perilymphatic space is visible.

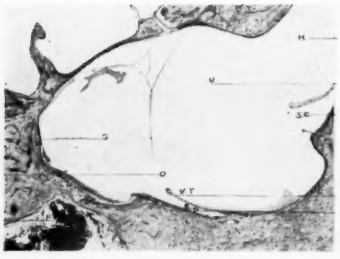


Fig. 4.

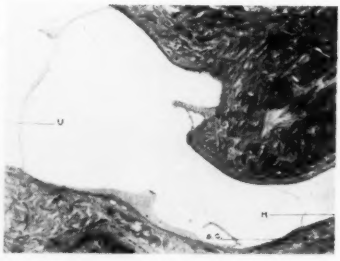


Fig. 5.

Fig. 4.—Case 1, right side. *E.D.*—Endolymphatic duct, Sinus I. *F*—Fundus of internal auditory meatus. *H*—Herniation of utricle into the inner extremity of the external semicircular canal. *O*—Opening between utricle and saccule. *S*—Saccule. *S.c.*—Opening of the inner extremity of the external membranous semicircular canal into the utricle. *U*—Utricle. *U.f.*—Utricular fold.

Fig. 5.—Case 1, right side. *H*—Herniation of the utricle into the common crus of posterior and superior vertical canals. *S.C.*—Opening of the common crus of the membranous canals into the utricle. *U*—Utricle.

The vestibular tests were as follows:

After rotation:

10 times to the right, nystagmus of 25 seconds duration.

10 times to the left, nystagmus of 23 seconds duration.

After calorization (water at 67° F.):

Right ear. Horizontal rotatory nystagmus after 52 seconds with past-pointing.

Left ear. Horizontal rotatory nystagmus after 40 seconds with past-pointing.

The patient went progressively downhill, he sustained spontaneous fractures of several ribs. He died about a week after admission.

The autopsy showed myeloma of the plasma cell type in the second to eighth ribs on the left side and in the tenth and eleventh thoracic vertebrae. There were many pathological fractures of the ribs on the left side. The autopsy also showed bilateral lobular pneumonia, chronic bilateral pyelonephritis. The brain, including the pons and the medulla, showed no gross or microscopic changes.

HISTOLOGICAL EXAMINATION OF THE TEMPORAL BONES

(serial sections)

Right Side

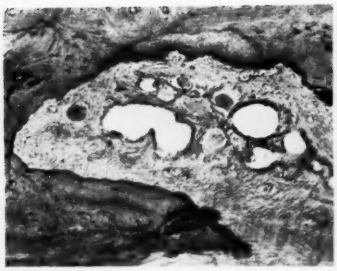
External Auditory Meatus and Drum Membrane. These showed no abnormalities.

Middle Ear. No abnormalities were found in the middle ear or its contents.

Mastoid. Mastoid and perilabyrinthine pneumatization is moderately well, apical poorly developed.

Inner Ear. The bony capsule is normal. The cochlear duct is extremely dilated, and the stretched membrane of Reissner is pushed to the wall of the scala vestibuli. The latter is almost completely obliterated but there are no signs of adhesions between the membrane and the endosteum of the scala. The dilated cochlear duct bulges through the helicotrema into the scala tympani. Corti's organ shows fairly well advanced postmortal changes but no definite signs of pathology. The stria vascularis looks normal. There is a slight diminution in the number of ganglionic cells and nerve fibers in the spiral ganglion in the lower half of the basal turn.

The cochlear aqueduct is permeable in its outer third, but filled in its inner two-thirds with loose connective tissue which contains



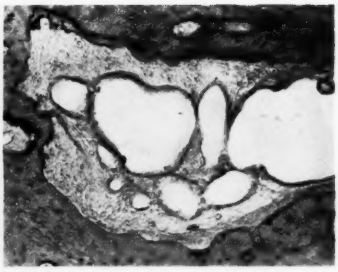


Fig. 6.—Case 1, right side. The subepithelial layer of well vascularized areolar connective tissue is completely absent.

Fig. 7.—Case 1, left side. The subepithelial layer of well vascularized areolar connective tissue is greatly reduced.

many thin-walled vascular spaces and, in some places, deeply blue-stained concrements, which evidently lie in the endosteal sheath of the duct (Fig. 9). The ductus reuniens is markedly dilated in its proximal part but the dilatation increases gradually towards its opening into the saccule.

The saccule itself is very markedly dilated and fills the larger part of the vestibule (Fig. 10). It covers the inner surface of the footplate of the stapes, extends around the utricle and bulges into the perilymphatic spaces of the inner end of the external semicircular canal. The macula sacculi shows only postmortal changes. The utricle is not noticeably dilated, its macula shows postmortal changes. The semicircular canals show normal width; the cristate ampullares show postmortal changes. In the peripheral parts of the cristae of the external and posterior vertical canal intra-epithelial cysts are seen. Some of these contain a colloidlike mass. Some subepithelial vesiculation is present in the semicircular canals and in the utricle and saccule. The saccular and the utricular ducts are short, the former slightly dilated.

The endolymphatic duct is moderately dilated in its proximal sinus, otherwise its lumen is normal. In the intermediate part the loose perisaccular tissue is completely absent, and the number of folds markedly reduced (Fig. 11). The lining epithelium is cuboidal. The fairly dense tissue surrounding the lumen contains numerous, sometimes ramified, cells, filled with coarse brown granules of hemosiderotic pigment. The terminal dilatation (saccus endolymphaticus proprius[6]) is not contained in the specimen because it had been re-

moved at the autopsy. The internal auditory meatus and its contents show no abnormalities.

Left Side

External Auditory Meatus and Drum Membrane. These show no abnormalities.

Middle Ear. The middle ear and contents show no abnormalities.

Mastoid. Not only the mastoid, but also perilabyrinthine and apical pneumatization is well developed.

Inner Ear. The changes are identical to those on the right side. The cochlear duct contains some pink-staining coagulum. The endolymphatic duct shows again in its intermediate dilatation a reduction in the number of folds and an absence of the loose perisaccular tissue. Pigmented cells are missing. Many of the recesses of the lumen contain pink-staining colloidlike masses. The terminal dilatation shows no abnormalities. The internal auditory meatus and contents show no abnormalities.

SUMMARY OF THE PATHOLOGICAL CHANGES IN THE INNER EAR

Right side. There is extreme dilatation of the cochlear duct with herniation through the helicotrema, very marked dilatation of the proximal half of the ductus reuniens, and extreme dilatation of the saccule which covers the footplate of stapes and bulges into the inner extremity of the external semicircular canal. The width of the utricle and the membranous semicircular canals is normal. There is slight dilatation of the saccular duct and of the proximal sinus of the endolymphatic duct. The perisaccular tissue is absent but there is an accumulation of pigmented cells in the subepithelial layers. There is a slight diminution in the number of ganglionic cells and nerve fibers in the lower half of the basal turn of the cochlea. The cochlear aqueduct is closed in its inner two thirds by loose reticular tissue which contains concretions.

Left side. The changes are the same as in the right ear. There are no pigmented cells in the fibrotic perisaccular tissue.

CASE 3.—W. S., male, 79 years old, was admitted Dec. 31, 1931. The patient was admitted with pneumonia. Little is known about his history. He was stone deaf and had dizzy spells in previous years. The examination showed the ear drums thickened; otherwise the findings were normal.

The patient died four days after admission. The autopsy showed bilateral pneumonia with abscess formation, arteriosclerosis of the aorta, the peripheral and coronary vessels, with fibrosis of the myocardium.

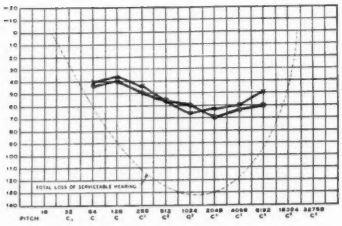


Fig. 8.—Audiogram showing hearing curve for Case 2.

HISTOLOGICAL EXAMINATION OF THE TEMPORAL BONES

(serial sections)

Right Side

External Auditory Meatus and Drum Membrane. The external auditory meatus shows no abnormalities. The mucosal layer covering the inside of the drum is thickened and fibrotic and shows extensive areas of calcification, particularly in the anterior superior quadrant of the drum. In some places bone formation is seen at the periphery of the calcified areas.

Middle Ear. There was an acute purulent otitis media. The niche to the round window shows some mucosal folds and bands. The ossicles and the muscles, as well as the facial nerve, are normal. There is no perilabyrinthine or apical pneumatization. The jugular bulb extends high up. The mastoid was not examined.

Inner Ear. The bony labyrinthine capsule shows some internal reconstruction in the periphery. The cochlear duct is extremely dilated and Reissners' membrane pushed to the wall of the scala vestibuli. The latter is obliterated throughout and the cochlear duct bulges through the helicotrema into the upper end of the scala tympani (Fig. 12). There are no adhesions between the endosteum of the scala vestibuli and the displaced membrane of Reissner. In some places the membrane is slightly detached from the wall. Corti's organ has completely disappeared in the lower basal turn and is reduced to a flat mound of cells in the upper basal turn. In the middle and upper turns, it is represented by a mound of cells in which the external and internal pillar cells are still recognizable. The tectorial membrane covers the remnants of Corti's organ. The stria vascularis

does not show definite pathological changes. There is a marked diminution in the number of ganglionic cells and nerve fibers in the lower half of the basal turn, less marked in its upper half.

The cochlear duct has a normal appearance and is patent throughout its entire length. The lower end of the cochlear duct is considerably dilated and bulges into the vestibule. It covers the lower half of the inner surface of the footplate of the stapes (Fig. 13). The ductus reuniens, the saccule and the utricle are also considerably dilated. The perilymphatic cysterna is reduced to a narrow space; the saccule fails to show any contact with the footplate of the stapes.

The macula sacculi and utriculi show marked postmortem changes. The nerve fibers appear normal in hematoxylin-eosin specimens. In a circumscribed area of the medial wall of the saccule the epithelium is detached from the underlying tissue by an accumulation of pale blue-staining mucoid fluid and forms an excrescence protruding into the lumen of the saccule. The utricular and saccular ducts are moderately dilated. The semicircular canals have normal width. The cristae ampullares show considerable postmortal changes, but the nerves appear normal. At the place where the ampullated ends open into the dilated utricle, a slight bulging of the utricle into the perilymphatic spaces of the ampullae is notable (Fig. 13).

The endolymphatic duct shows normal width. In the intermediate part, there is a moderate number of folds, covered with a rather flat epithelium. The subepithelial layer of loose areolar tissue is present. The recesses contain small colloidlike concretions. The internal auditory meatus and its contents appear normal.

Left Side

External Auditory Meatus and Drum Membrane. These show no pathology.

Middle Ear. There are a few mucosal folds and bands in the niche to the round window. There is no perilabyrinthine or apical pneumatization. The mastoid is not shown in the sections.

Inner Ear. The labyrinthine capsule shows internal reconstruction in the peripheral layers. The cochlear duct is markedly dilated and completely fills the scala vestibuli, but there is no bulging of the duct through the helicotrema into the upper part of the scala tympani. The organ of Corti shows a very poor state of conservation. The stria vascularis is normal. The spiral ganglion and the nerve fibers show the same changes as in the other ear. The dilated lower

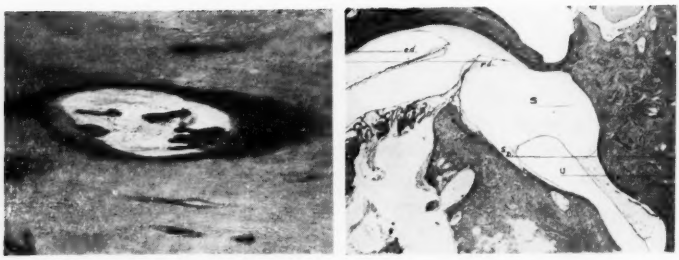


Fig. 9.—Case 2, right side. Inner third of the cochlear aqueduct, filled with loose connective tissue which contains deeply blue-stained concrements.

Fig. 10.—Case 2, right side. *c.d.*—Cochlear duct. *r.d.* ductus reuniens. *S*—Saccule. *s.d.*—Saccular duct. *U*—Utricle and common crus of posterior and superior vertical canals.

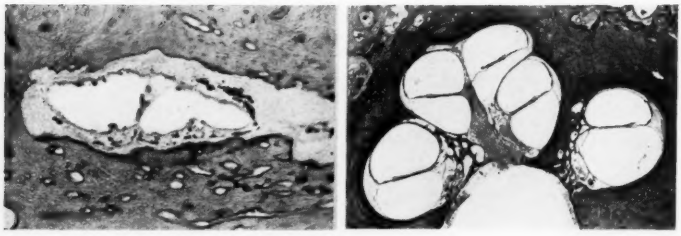


Fig. 11.—Case 2, right side. The loose "perisaccular tissue" is replaced by fibrous connective tissue which contains numerous cells filled with hemosiderotic pigment.

Fig. 12.—Case 3, right side. The cochlear duct is extremely dilated and herniated through the helicotrema into the scala tympani. The scala vestibuli is completely obliterated.

end of the cochlear duct bulges into the vestibule. The cochlear aqueduct is normal and patent throughout its length. The saccule, the utricle and the semicircular canals show little if any dilatation. The maculae and the cristae show only postmortal changes. The endolymphatic duct and its terminal dilatations show a normal width. In the intermediate part there are only a few folds and a complete absence of the loose subepithelial tissue. The internal auditory meatus and its contents show no pathological changes.

SUMMARY OF THE PATHOLOGICAL CHANGES IN THE INNER EAR

Right side. There is extreme dilatation of the cochlear duct which herniates through the helicotrema and bulges into the vestibule and covers the lower half of the stapes' footplate thus displacing the saccule. There is marked dilatation of the ductus reuniens, the saccule and the utricle, with a slight bulging of the latter into the perilymphatic spaces of the ampullated ends of the semicircular canals. Degenerative changes of Corti's organ in the basal turn are shown, with complete disappearance of the organ in the lower half of this turn. There is diminution in the number of cells of the spiral ganglion and of the nerve fibers in the basal turn. Also there is marked subepithelial vesiculation in the medial wall of the saccule; reduction in the number of folds in Sinus II of the endolymphatic duct, but presence of the loose perisaccular tissue.

Left side. There is marked dilatation of the cochlear duct, but no herniation through the helicotrema. The width of the other parts of the endolymphatic system is normal. Corti's organ is poorly conserved and there are marked postmortal changes in the other end-organs. There is diminution in the number of spiral ganglion cells and nerve fibers in the basal turn. The loose "perisaccular" tissue is completely absent.

COMMENT

The anatomical findings in these three cases are very similar to each other and to those in the previously reported observations. In all of them a dilatation of the endolymphatic system was the most striking feature.

In Case 1 the changes were confined to one side; in Cases 2 and 3 both sides were affected. The degree of dilatation varied in the three cases and also on both sides in the same case (Case 3). In one instance (Case 3, left side) the dilatation was confined to the cochlear duct. In the observations of others, other parts, with the excep-

Fig. 13.—Case 3, right side. *c.d.*—Cochlear duct. *F*—Footplate of stapes. *r.w.*—Membrane of the round window. *s.t.*—Scala tympani. *U*—Utricle.

tion of the semicircular canals, were also dilated. The cochlear duct was extremely dilated and herniated through the helicotrema into the scala tympani in all three cases with the exception of the left side of Case 3. Here the dilatation was less marked and there was no herniation present. The dilatation of the saccule was always well marked. The dilatation of the utricle varied in its extent; it was well marked in Case 1, absent in Case 2 and on the left side of Case 3, but marked on the right side of Case 3. The dilated utricle protruded in Cases 1 and 3 (right side) into the perilymphatic spaces of the semicircular canals, but the degree of these herniations varied in extent. In Case 2 a herniation of the saccule into the inner extremity of the external semicircular canals was seen in both ears. A marked distortion of the ampullated ends due to these herniations was not noticed.

Among the previously reported cases, seven showed unilateral and three bilateral changes. Thus, out of the total of 13 known cases, 8 were unilateral and 5 bilateral. The relative frequency of bilateral changes contradicts the statement of Rollin,[30] that the disease is nearly always unilateral. In some of the cases in the literature, only the cochlear duct, in others the cochlear duct and the saccule,

in the majority the cochlear duct as well as the utricle and the saccule were dilated. Usually the dilatation of the saccule was more marked than that of the utricle. Twice a herniation of the saccule into the inner extremity of the external semicircular canal had occurred;[18] once a protrusion of the utricle into several canals on both sides;[24] once into the ampulla of the superior vertical canal, and once from the inferior part of the utricle into an undescribed area.[30] The fact that the cochlear duct was dilated in all of the cases, the saccule in most of them, the utricle in many of them and the semicircular canals in none, is usually explained by differences in the thickness of the walls of these structures. The end-organs, particularly the organ of Corti, showed such considerable postmortal changes that it is impossible to determine whether true pathological changes were simultaneously present or not. Only the diminution in the number of ganglionic cells and nerve fibers of the spiral ganglion, is unquestionably due to true pathologic changes.

The findings of the other authors are neither uniform nor conclusive. Mostly the organ of Corti is described as normal or in a state of "hypotonic collapse" or as "hypertonic."[30] Once the hair cells were degenerated, but this was possibly only a postmortal change.[24] In some cases an increased retention of hematoxylin was found in the cells of Corti's organ.[18]

The maculae and the cristae were in most instances normal; only once[18] did they show a marked tendency to hematoxylin retention. The subepithelial vesiculation which was found in the medial wall of the saccule in Case 3 is of doubtful pathological significance; it was also frequently found in normal cases by Hallpike and Cairns.

If we regard the dilatation of the endolymphatic system as the essential morphological feature in Ménière's symptom complex, two of the cases reported before 1938 evidently belong to this group.

In Brunner's[9] case Paget's disease was found in both temporal bones. The left inner ear showed a marked dilatation of the cochlear duct with herniation through the helicotrema into the scala tympani, and a dilatation of the saccule and of the medial part of the utricle. Corti's organ is described as degenerated and the stria vascularis as atrophic. There was an atrophy of the spiral ganglion and of the cochlear fibers, most marked at the base of the cochlea. The maculae and the cristae were also regarded as atrophic. The cochlear aqueduct was filled with reticulated tissue which contained concretions. The endolymphatic duct was patent. On the right side the dilatation

was confined to the medial part of the utricle. The cochlear aqueduct was patent but otherwise the findings were the same as on the other side.

In the case described by Wittmaack,[34] a neuroma was found which originated from the ramifications of the cochlear nerve within the basal cochlear turn. It had grown into the scala tympani and then into the lumen of the cochlear duct. The picture showed that the cochlear duct was dilated and Corti's organ in a state of "posthydropic" degeneration. The spiral ganglion and the nerve itself showed only a moderate diminution of nerve fibers and of spiral ganglion cells. The maculae and the cristae were normal. The condition of the endolymphatic duct is not mentioned. The cochlear aqueduct contained concretions in the narrowest part of its lumen.

The histological report in the case of Berggren[8] is not given in enough detail to permit definite conclusions. According to the report, no dilatation was present.

The cases of Alexander and Manasse[1] and of Videbech[33] did not present the characteristic clinical picture of the group of cases which is discussed here and they are, therefore, omitted in our discussion.

The uniformity of the morphological findings in Ménière's symptom complex is very striking. The dilatation of the endolymphatic system is evidently due to an increased endolymphatic pressure. The absence of changes in the perilymphatic space leads to the conclusion that the cause for this increase in pressure must be located within the endolymphatic system itself. The complete absence of signs of inflammation precludes the possibility of an interpretation of the changes as inflammatory, as some kind of serous labyrinthitis. But beyond that, the histological findings fail to give any hint as to the mechanism by which the changes were brought about.

Our knowledge of the normal physiology of the labyrinthine fluids is limited. According to Guild,[16, 17] the endolymph is produced in the stria vascularis; according to Wittmaack[34] the greatest part is produced in the stria, but some endolymph is also produced in the organ of Corti, in the maculae and the cristae, in the areas of higher epithelium at the periphery of the cristae, and in the so-called atypical epithelial formations of the vestibule. The resorption of the endolymph takes place, according to Guild, in a certain part of the endolymphatic sac into the capillaries of the loose perisaccular tissue. According to Wittmaack resorption takes place mainly in this area but also to some extent by way of diffusion through the membrane

of Reissner into the scala vestibuli. No matter which theory is correct, the dilatation of the endolymphatic system could be due either to an overproduction or a diminished resorption of the endolymph or to a combination of both of these factors. There must not necessarily be a quantitative disturbance in the production of the endolymph, but possibly there could be a qualitative disturbance, such as the production of an endolymph of a different physicochemical constitution.[10] It is conceivable that a continuous secretion of endolymph of abnormally high ionic concentration will lead to a dilatation of the endolymphatic spaces by osmotic attraction of water molecules through its membranous walls from the surrounding perilymph.[18]

Changes in the secretory activity of the stria vascularis or perhaps of the other areas are primarily functional disturbances, and it can not be expected that they will manifest themselves in marked morphological changes, at least not in the earlier and possibly not in the later stages.

Under these circumstances absence of morphological changes can not be regarded as proof of normal functional integrity. In some cases regressive changes were found, but these were neither uniform nor sufficiently significant to be impressive. A fibrosis of the loose, vascular connective tissue which normally surrounds the resorptive area of the endolymphatic duct (Sinus II[3]) has been regarded as morphological evidence of a disturbance of the resorptive mechanism.[18, 30] A marked fibrosis on the affected side and a somewhat less pronounced fibrosis on the healthy side were found in Case 1 of this paper. Case 2 showed a definite fibrosis on both sides, with accumulation of hemosiderotic pigment, apparently due to an old hemorrhage on one side. In Case 3 a fibrosis was seen only on the less affected side. The resorptive epithelium did not show definite and convincing changes. Fibrosis of the perisaccular tissue was found in most of the cases reported in the literature. On the other hand, it was present in some normal temporal bones examined by Hallpike and Cairns. These two authors feel that these changes represent anatomical variations which, because of the retardation of the resorption of the endolymph, may act as a predisposing factor in bringing about the dilatation. Rollin states that the fibrosis is either due to local inflammatory changes or is secondary to degenerative changes in the resorptive epithelium.

Clinical evidence, such as the therapeutical response to certain drugs, and the results of animal experiments, have led many authors to assume that the Ménière attacks in this group of cases were the

result of circulatory disturbances in the labyrinthine vessels which produced an increase in the endolymphatic pressure. Soon it was recognized that the mechanism of the attacks was evidently not the same in all cases. In some of them a primary vasoconstriction, followed by a vasodilatation[23] had been assumed, in others a primary capillary vasodilatation with increased capillary permeability (angioneurotic edema, Quincke,[29] Kobrak;[20, 21] allergy, Duke,[13] Dederding[12] and others; a disturbance in the water balance, Mygind and Dederding;[26] or electrolyte metabolism, Furstenberg[15]).

Some authors draw a very sharp distinction between the cases supposedly caused by primary vasoconstriction and those with primary vasodilatation[4] while others, like Vernet[32] and Kobrak,[20, 21] feel that in some cases both factors might be involved. The assumption of primary changes in the secretory mechanism with changes in the resorptive mechanism as a predisposing factor seems more plausible than the opinion expressed by Rollin, that the changes in the resorptive mechanism are the primary ones. It is difficult to explain the occurrence of repeated attacks with a steadily progressive condition such as a fibrosis of the perisaccular tissue. This, apparently was realized by Rollin and he conceded that possibly an intermittent increase in the production of endolymph might accompany the "retention-hydrops." It may be mentioned in this connection that the differences in the extent of the dilatation of the various parts of the endolymphatic system need not necessarily be caused solely by differences in the dilatability of their respective walls. It is conceivable that they indicate that the changes start primarily in the stria vascularis and lead in the beginning only to a dilatation of the cochlear duct. The narrowness of the communicating canals could possibly prevent the dilatation of the utricle and the saccule for some time.

The explanation of the clinical signs and symptoms of the condition is still controversial. According to Hallpike and Cairns[18] the membranous labyrinth is a closed fluid system and the mechanism for the secretion and the absorption of fluid is located within its walls. Surrounding it is the perilymph which reaches the perilymph spaces through the cochlear aqueduct from the subarachnoid space. Any volume increase in the endolymph will be met by an expansion of its thin and elastic membranes and by the expulsion, through the helicotrema and the cochlear aqueduct, of a corresponding volume of perilymph. The primary resulting pressure change in the fluid system as a whole will be negligible. If, however, the endolymphatic fluid system becomes fully dilated, its elastic membranes will everywhere be brought into contact with the rigid bony wall except at the heli-

cotrema. At this point Reissner's membrane bulges into the scala tympani and this relatively limited space is the only remaining area for elastic expansion. When the dilatation of the endolymph system has attained its maximum degree, the fluid system of the membranous labyrinth becomes at once affected and extremely sensitive in its pressure response to volume changes of the endolymph. The attacks may be thus caused by rapidly initiated bouts of asphyxia of the vestibular end-organs, because of rapid rises in the fluid pressure in response to relatively small volume increases in the endolymph. In the intervals a chronic condition of deficient function of the labyrinth is present because of increased endolymph pressure and the resulting anoxemia of its end-organs. In the organ of Corti, at least in the earlier stages, no anoxemia will occur, because the organ of Corti does not contain capillaries. But some degree of structural disintegration by pressure on its sensory elements is conceivable, though its exact nature and extent is unknown.

According to Rollin[30] a herniation of the cochlear duct through the helicotrema into the scala tympani causes an interruption of the communication between the perilymphatic spaces to either side of this point. Any further dilatation of the endolymphatic system will lead to an increase in the perilymphatic pressure in the scala vestibuli and the semicircular canals. This increased pressure will act upon and stimulate the nerve endings. In addition, due to the close relationship of the dilated saccule to the utricle, variations in the pressure within the saccule will immediately affect the utricle. Only sudden fluctuations in pressure, not a slow and steady increase, will cause a stimulation of the end-organs. When a complete closure of the helicotrema and a permanent overpressure without sudden fluctuations has been established, the attacks will cease. The disturbance in hearing results from the dilated saccule which is pushed towards the stapes footplate and the annular ligament, and this pressure interferes with the motility of the stapes.

Lindsay[24] denies that the disturbances of function are caused by the increased endolymphatic pressure acting directly on the sensory epithelium, because there is a mechanism to preserve pressure equilibrium between the perilymph and the cerebrospinal fluid, and because in brain tumors or other conditions in which the cerebrospinal pressure is markedly increased and fluctuating, with the same amounts of increase and fluctuations present in the endolymph, Ménière attacks are neither frequent nor characteristic. The attacks are explained by Lindsay as caused by the herniation of the utricle into the semicircular canals with subsequent distortion of the wall of the ampullae.

The distortion interferes with the normal function of the cupula and explains both the attacks of vertigo and the depression of the caloric excitability in the latter stages. The auditory disturbances are caused by the distortion of the saccule and the membrane of Reissner, both of which may interfere with the sound transmission in the column of fluid in the cochlea.

It seems difficult to decide which of these theories is the most probable. All the authors assume that in human beings the pressure equilibrium between cerebrospinal fluid and perilymph is brought about and maintained through the cochlear aqueduct in a similar manner as in experimental animals. But this is not necessarily true. According to Meurman[25] the physiological significance of the aqueduct in man has not been definitely clarified. The canal is in human beings very narrow, relatively much narrower than in animals, e.g., rabbits. It is frequently filled with dense connective tissue and sometimes with bone. It seems probable that in such cases a quick reduction of the perilymphatic pressure, or in instances with osseous obliteration, any reduction at all could be brought about by way of the aqueduct. Meurman thinks that the peculiar condition of the human aqueduct is probably compensated for by the relatively greater width of the perivascular spaces of the modiolus. In his opinion, the larger part of the perilymph seems to originate in the vessels of the modiolus and to reach the perilymphatic spaces by way of diffusion through the perivascular spaces. Only the smaller part of the perilymph seems to reach the inner ear by way of the cochlear aqueduct.

If this is true it seems reasonably clear that an occlusion of the aqueduct with connective tissue or concretions can hardly be regarded as sufficient explanation for the development of Ménière attacks. Future investigations, however, will have to show if, and to what extent, anatomical variations within the duct may act as predisposing factors for the development of the attacks.

Thus, the question of how an increase in the intracranial pressure will affect the intralabyrinthine pressure in man is very complex and can, at the present time, hardly be answered satisfactorily to all. Furthermore, it seems conceivable that a pressure increase originating in the endolymphatic system might have a physiological effect different from that resulting from an increase transmitted from the perilymph. According to Zange[36] the aqueductus cochleae is comparable to a curved capillary tube and the viscosity of the cerebrospinal fluid, particularly under pathological conditions, is high. Both factors pre-

vent the transmission of short sudden pressure increases to the perilymphatic space. Only longer lasting increases are gradually transmitted. In the meantime some perilymph is resorbed by the perilymphatic tissue and and the pressure remains, as a rule, unchanged. All the authors with the exception of Hallpike and Cairns[18] agree that during the attacks a stimulation of the vestibular system takes place. Hallpike and Cairns assume that the functional state of the diseased labyrinth is lowered in the entire course of Ménière's "disease" and is particularly low during the attacks. According to these authors, the vestibular symptoms occurring during the attacks are due to a vestibular imbalance resulting from predominance of the tonus of the healthy labyrinth over that of the diseased one.

The analysis of the vestibular reactions in certain cases of Ménière's symptom complex throws some light upon this question. In Case 1 of this paper the caloric irritability in face-front position was completely lost, not only on the diseased but also on the healthy side, and the response to rotation was considerably reduced. Loss or marked reduction of the vestibular irritability in unilateral Ménière's symptom complex not only on the affected but also on the clinically normal side has also been seen in other cases.

A particularly interesting observation has been reported by Crowe.[10] In a man of 61 years of age with a clinically affected right ear, the caloric tests were normal on both sides before intracranial division of the right vestibular nerve. Shortly after the operation there was no response on either side, but two and a half years later there was no response on the operated side and incomplete and very active response on the other side. In this case a permanent loss of the vestibular function was accompanied by a transient loss on the opposite side.

Similar anomalies in the vestibular function have been known for a long time in inflammatory diseases of the labyrinth. In certain cases, after destruction of one labyrinth, the vestibular reaction of the other ear is permanently[5] or temporarily[7] lost without any changes in the cochlear function in the normal ear. One case has been reported[2] in which a temporary loss of vestibular function due to a serous labyrinthitis of one ear was accompanied by a temporary loss of caloric response and a marked reduction of the response of the other ear to rotation.

The best way to explain these anomalies is with changes in the central regulatory mechanism of the vestibular apparatus, possibly comparable to those occurring in Ruttin's[31] compensation reaction.

The anomalies occurring in Ménière's cases can be explained in a similar way by a reflectory inhibition of the function of the healthy vestibular apparatus. The absence of morphological changes in the vestibular centers in Case 1 of this paper indicates that the changes were of a functional nature.

The fact that the caloric response was completely lost but the rotatory response only greatly reduced could be explained by the widely accepted assumption that rotation represents a stronger stimulation of the labyrinth than calorization. The above-mentioned cases demonstrate that in certain instances the loss of the vestibular function of one ear is accompanied by a reflex inhibition of the vestibular function of the other ear. This inhibition has never been observed in cases in which the contralateral labyrinth was in a state of stimulation. This fact could possibly support the assumption that, at least in certain cases, Ménière attacks represent a depression rather than a stimulation of the vestibular function. On the other hand, the histological pictures do not preclude the possibility of a stimulation of the ampullae during the attacks either by the dilated and herniated saccule or utricle. The dilatation of the endolymphatic system as seen in our specimens characterizes the interval between the attacks and the late stages of the disease. The critical anatomical changes which are present during the attacks themselves are not known, but it seems fairly reasonable to assume that the endolymphatic pressure is still further increased, and the dilatation more marked, than during the intervals.

The hearing loss in Ménière's symptom complex, when present, is clinically characterized by a more uniform involvement of the entire tone range and wide fluctuations in the threshold, particularly in the lower and middle range. Bone conduction may be relatively good, particularly for the lower tones, and the upper limit frequently may be fairly well preserved. Recruitment of loudness[14] is usually partial[24] but was complete in some of our own clinical observations; this is regarded as a sure criterion for neural deafness. Intermittent diplacusis binauralis dysharmonica is a frequent finding. In advanced cases the hearing loss is much more marked, the high notes become more and more involved and the fluctuations in hearing decrease and disappear, with increasing deafness.

The wide fluctuations in the threshold in not too far progressed cases indicates that the hearing loss must be due to a large extent to reversible changes. This is confirmed by the fact that Corti's organ, as a rule, showed relatively little if any histological changes. The

opinion expressed by Lindsay[21] that the auditory disturbances are caused by the distortion of the saccule and the membrane of Reissner, which interferes with the sound transmission in the column of fluid in the cochlea, seems a reasonable explanation. A temporary more or less complete fixation of the stapes due to pressure from the dilated saccule, as Rollin[30] assumes, can hardly explain the disturbance in hearing. Rollin's main argument in favor of his theory, besides his histological findings, is the fact that the results of the functional examination with tuning forks in the cases reported by this author were "strikingly similar" to those obtained in cases of conduction deafness. He found considerable reduction of hearing for the low notes with relatively good hearing for high notes. There was no marked "absolute lengthening" of bone conduction and the Weber test was not lateralized to the affected or more affected ear. Rollin concludes that the hearing disturbance in Ménière cases is a conduction deafness due to impaired motility of the stapes. The audiograms taken in four of the histologically examined cases (Case 2 of Hallpike and Cairns,[18] the case of Hallpike and Wright,[19] and Cases 1 and 2 of this paper) and in many of the clinical observations show a more uniform loss of hearing for all frequencies. On examination with tuning forks alone these cases, too, most probably would have shown an apparently greater loss for the low notes than for the high ones. According to Langenbeck[22] the maximal loudness for the low forks is only little above the normal threshold of hearing, whereas the maximal loudness for the high forks is much above the threshold. A given amount of hearing loss, therefore, will appear to affect the perception of the low tuning forks to a relatively greater extent than the perception of the high forks, unless careful decibel estimates are obtained. It must be mentioned that this has nothing to do with the fact that the low forks are heard longer than high forks. This may be due to the lesser dampening of the low forks or to a faulty manufacture. In most Hartmann sets 512 d.v. is heard longer than the others.

The question of an "absolute lengthening" of bone conduction shall not be discussed. It will only be mentioned that a real lengthening of bone conduction is very rare in cases of stapes ankylosis. Of much greater importance for the differentiation between conduction- and perception-deafness than tuning fork tests is the loudness balance test.[14] The Ménière cases show incomplete or even complete recruitment of loudness, a fact which proves that the hearing loss in these cases is partially or completely caused by disturbances in the perceptive, and not in the conductive, mechanism.

But even if Rollin's argumentation were true, it does not explain the hearing loss in those instances in which the dilatation of the saccule was not marked enough to impair the motility of the stapes.

The progressive loss in hearing and the gradual involvement of the high notes in the later stages of the disease is best explained by secondary degenerative changes in the perceptive system. Histologically, we find in these cases a diminution in the number of the ganglionic cells and nerve fibers of the spiral ganglion. Sometimes also Corti's organ in the basal turn shows degenerative changes. The findings are similar to those in old-age deafness and certain forms of chronic progressive deafness of degenerative or toxic origin. In some of the cases, e.g., Case 3 reported in this paper, the possibility of a coexistant old-age deafness must be considered; in others the changes are probably secondary to the intralabyrinthine changes. It is conceivable that they are the result of the same vasomotor disturbances which were supposedly the cause of the intralabyrinthine changes. The displacusis is explained as the sequela of the generalized stretching of the basilar membrane due to the increased endolymphatic pressure, with a subsequent change in the natural frequency distribution of its tonal components.[18]

The histological findings in all the reported cases do not reveal any facts which could fully explain the mechanism of the tinnitus. The fact that it may persist even after complete section of the eighth nerve indicates that, at least in these instances, it may be due to retrolabyrinthine changes.

No matter what the final explanation of the clinical picture, the fact remains that in all the examined cases of Ménière's symptom complex convincing evidence of an increased endolymphatic pressure was found. This must be kept in mind when one attempts to evaluate certain therapeutic measures used in this condition. The conservative treatment will not be discussed in this paper because the histological findings did not demonstrate any new facts concerning the etiology of the condition or the mechanism by which the attacks are brought about.

Among the operative methods two are particularly interesting: the intracranial division of the vestibular nerve,[11] and the opening of the endolymphatic sac.[27, 28] Dandy's operation is purely palliative. In successful cases it eliminates the dizziness completely. The endolymphatic pressure remains unchanged and the cause for the

attacks is not eliminated. Most probably the attacks continue, but due to the division of the nerve, they do not produce dizziness. The progress of the deafness and of the tinnitus is not influenced or stopped. Portmann's operation is also palliative, but is evidently a more physiological approach to the problem. By reducing the endolymphatic pressure it also eliminates in successful cases the attacks of dizziness, but, in addition, it tends to restore the original condition of the entire endolymphatic system. It is to be expected that in the not too far progressed cases a lasting improvement in hearing will result from this procedure; but, up to the present, audiometric examaminations of cases operated upon by this method are missing and so we can not properly evaluate the effect upon the hearing. The cause for the attacks is not eliminated by this operation. But as long as the opening in the endolymphatic sac is patent, the endolymphatic pressure will hardly increase during the etiological episodes, and only slight, if any, clinical manifestations will ensue.

SUMMARY AND CONCLUSIONS

1. A detailed description of the histological findings in the labyrinth in three cases of Ménière's symptom complex is given.

2. The findings were strikingly similar to those in the ten already published cases. In all of them a dilatation of the endolymphatic system was the most prominent feature.

3. The extent of the dilatation varied. Dilatation of the cochlear duct was always present; the semicircular canals remained free from dilatation.

4. The end-organs in the three cases showed postmortal, but no other definitely pathological, changes.

5. A fibrosis of the "perisaccular" tissue was present in all instances, was marked once in the less affected ear only, and once equally marked in the unaffected side.

6. The literature is reviewed and the various theories of the pathogenesis of the condition discussed.

7. Disturbances in the secretion of the endolymph are most probably the primary cause, with fibrosis of the "perisaccular" tissue as a predisposing factor. The role of the cochlear aqueduct and the significance of its peculiar structure in man for the physiology of the labyrinthine fluids is pointed out.

8. The theories which try to explain the clinical signs and symptoms are critically reviewed.

9. The vestibular symptoms are possibly of dual origin, and in some instances caused by a lowered, and in others by an increased, vestibular function on the affected side.

10. The auditory disturbances are possibly due to the distortion of the saccule and of the cochlear duct which interferes with the sound transmission in the column of fluid in the cochlea.

11. It is pointed out that among the operative procedures, opening of the endolymphatic sac seems at present to be the most physiological and sane approach.

10 East 85th Street

180 Fort Washington Avenue

REFERENCES

1. Alexander, F. and Manasse, P.: Über die Beziehungen der chronischen, progressiven, labyrinthaeren Schwerhoerigkeit zur Ménièreschen Krankheit, Zeitschr. f. Ohrenheilk. 55:183, 1908.

2. Altmann, F.: Zur Frage der reflektorischen Ausschaltung des Vestibularapparates, Mschr. f. Ohrenheilk. 70:709, 1936.

3. Anson, B. J. and Nesselrod, J. P.: Endolymphatic and Associated Ducts in Man, Arch. Otolaryng. 24:127, 1936.

4. Atkinson, M.: Observations on the Etiology and Treatment of Ménière's Syndrome, J. A. M. A. 116:1753, 1941.

5. Barany, R.: Untersuchungen über den vom Vestibularapparat ausgeloesten Nystagmus, Mschr. f. Ohrenheilk. 40:193, 1906.

6. Bast, T. H.: The Endolymphatic Ducts and Valve, Anat. Rec. 68:75, 1937.

7. Beck, O.: Ausschaltung des linken Vestibularapparates bei eitriger Labyrinthitis rechts. Wiederkehr der Funktion links nach Labyrinthoperation rechts, Mschr. f. Ohrenheilk. 46:288,1912.

8. Berggren, St.: Die Bedeutung von Golls und Burdachs Kernen bei Ménièreschen Anfaellen, Acta otolaryngol. 15:234, 1931.

9. Brunner, H.: Über einen Fall von Pagetscher Erkrankung, Mschr. f. Ohrenheilk. 56:810, 1922.

10. Crowe, S. J.: Studies Based on Examination Made before and after Intracranial Division of the Eighth Nerve, Medicine 17:1, 1938.

11. Dandy, W. E.: Ménière's Disease, Arch. Surg. 16:1127, 1928.

12. Dederding, D.: Morbus Ménièri, Acta otolaryngol. Supp. X, 1928.

13. Duke, W. W.: Ménière's Syndrome Caused by Allergy, J. A. M. A. 81:2179, 1923.

14. Fowler, E. P.: Method for Early Detection of Otosclerosis, Arch. Otolaryngol. 24:731, 1936.

15. Furstenberg, A. C., Lashmet, F. H., and Lathrop, F.: Ménière's Symptom Complex: Medical Treatment, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 43:1035, 1934.

16. Guild, S. R.: Observations upon the Structure and Normal Contents of the Ductus and Saccus Endolymphaticus in the Guinea Pig, Am. J. Anat. 39:1, 1927.

17. Guild, S. R.: The Circulation of the Endolymph, Am. J. Anat. 39:57, 1927.

18. Hallpike, C. S. and Cairns, H.: Observations on the Pathology of Ménière's Syndrome, J. Laryngol. & Otol. 53:625, 1938.

19. Hallpike, C. S. and Wright, A. J.: Histologic Changes in Temporal Bones of Case of Ménière's Disease, J. Laryngol. & Otol. 55:59, 1940.

20. Kobrak, F.: Die Gefaesserkrankungen des Ohrlabtrinthes und ihre Beziehungen zur Ménièreschen Krankheit, Berl. klin. Wschr. 57:185, 1920.

21. Kobrak, F.: Die vasculaeren Erkrankungen des Labyrinthes, Handbuch d. Neurologie des Ohres hrsg. v. Alexander & Marburg. Vol. II, part 1, p. 535, 1928.

22. Langenbeck, B.: Das elektro-akustische Hoerpruefungs-und Verbesserungsgeraet, Zeitschr. f. Hals-usw. Heilk, 40:201, 1936.

23. Lermoyez, M.: Le vertige que fait entendre, Presse med. 27:1, 1919.

24. Lindsay, J. R.: Labyrinthine Dropsy and Ménière's Disease, Arch. Otolaryngol. 35:853, 1942.

25. Meurman, Y.: Zur Anatomie des Aquaeductus cochleae, nebst einigen Bemerkungen über dessen Physiologie, Acta Soc. med. denn. duodecim (Ser. B) 13:1, 1930.

26. Mygind, S. H. and Dederding, D.: Pathogenesis of Ménière's Disease and Kindred Diseases, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 47:938, 1938.

27. Portmann, G.: The Saccus Endolymphaticus and an Operation for Draining the Same for the Relief of Vertigo, Jour. Laryngol. 42:809, 1927.

28. Portmann, G.: Vasomotor Affections of the Internal Ear, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 38:69, 1929.

29. Quincke: cit. Portmann, G., Vasomotor Affections of the Internal Ear, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 38:69, 1929.

30. Rollin, H.: Zur Kenntnis des Labyrinthhydrops und des durch ihn dedingten Ménière, Hals-Nasen-Ohrenarzt (Teil I) 31:73, 1940.

31. Ruttin, E.: Funktionspruefung des Vestibularapparates, Handbuch der Hals-Nasen-Ohrenheilk. hrsg. v. Denker und Kahler, Vol. VI, Berlin-Muenchen, Springer-Bergmann, 1926, p. 995.

32. Vernet, M.: Le vertige et son traitement par l'adrenaline, Presse med. 28:462, 1920.

33. Videbech, H.: Affection du labyrinthe se presentant sous le traits du syndrome de Ménière, Acta otolaryngol. 22:51, 1935.

34. Wittmaack, K.: Über den Tonus des Sinnesendstellen des Innenohres; die Ménièresche Krankheit im Sinne der Tonuslehre, Arch. f. Ohrenheilk. 124:177, 1939.

35. Yamakawa, K.: Über die pathologische Veraenderung bei einem Ménière-Kranken, Zeitschr. f. Oto-Rhino-und Laryngologie 34:181, 1938.

36. Zange, J.: Pathologische Anatomie und Physiologie der mittelohrentspringenden Labyrinthentzündungen, Wiesbaden, Bergmann, 1919.

VII

THE REACTION OF THE NORMAL AND THE ALLERGIC SINUS TO VIRULENT PNEUMOCOCCI*†

IRA FRANK, M.D.
MARGERY BLAHD, M.D.
AND
KATHARINE M. HOWELL, M.D.

CHICAGO

Whether individuals suffering from allergic diseases are more or less resistant to pathogenic organisms is a subject on which there is no general agreement.

Vaughn and Derbes,[1] in a statistical study of all types of allergy, found no significant difference between allergic and nonallergic groups in the incidence of acute infectious diseases.

According to Duke[2] individuals with hay fever and asthma are predisposed to acute infections of the upper respiratory tract. Rackeman and Colmes[3] have the impression that allergic individuals are more susceptible than nonallergic individuals to colds, tuberculosis and acute infectious diseases. On the other hand, Feinberg[4] found fewer acute infections in a group of asthmatics than in a group of controls. However, there is little experimental confirmation in the literature concerning either of these opinions.

The object of our experiments was to determine whether a specific organ which is the seat of chronic allergic changes, is more or less susceptible than a normal organ to acute infection produced by pathogenic organisms. In this connection, Cannon and Hartley,[5] in attempting to learn whether the reaction of allergy can act as a protective mechanism, strongly sensitized a group of rabbits to egg white, until they were Arthus-positive. Highly virulent pneumococci in five per cent egg albumen solution were injected subcutaneously into these sensitized animals, as well as into an equal number of normal controls. The animals of both groups expired after the

*From the Departments of Otolaryngology, Pathology and Bacteriology of Michael Reese Hospital, Chicago, Illinois.

†Aided by a grant from the Michael Reese Research Foundation.

same length of time. Extensive acute allergic inflammation‡ was produced in the experimental group. Apparently the accelerated allergic state neither hindered nor promoted the spread of infection.

The maxillary sinus was chosen for our experiments because it is frequently the site of allergic involvement; and a chronic type of allergic change was produced, to simulate more closely the allergy of the sinuses in man.

METHODS

Half-grown healthy rabbits weighing 1.5 to 2.5 kg. were the experimental animals. These were sensitized by four to five injections into the sinuses (maxillary) at five-day intervals of a five per cent aqueous solution of egg white in conjunction with agar. Details of this method of sensitization appear in a previous report.[6]

Skin tests for hypersensitivity to egg albumen were performed on each animal following the final sensitization injection. One cc. of the egg white solution was injected into the skin of the abdomen following careful removal of the hair.

At intervals of 3 to 15 days after the last sensitization injection, various amounts of a pneumococcus culture highly virulent to rabbits were injected into the sinuses of sensitized and normal control animals. In the case of six experimental rabbits and three controls the organism injection was repeated two days after the original injection.

From one to two days after the administration of the pneumococci the animals were sacrificed by intravenous air injection.

Specimens were taken for biopsy from the sinus membranes by means of a sharp cork bore. These pieces of tissue were fixed in formalin; paraffin sections were made and stained with hematoxylin and eosin.

EXPERIMENTS

Equivalent numbers of pneumococci in agar were injected into the sinuses of 19 sensitized animals and 16 normal control rabbits. All test animals were systemically highly sensitive to egg white, as evidenced by skin tests. The majority responded with the Arthus reaction; the rest developed large red swollen areas in the skin site of testing. Sections from the sinuses were studied by two individuals, and the relative degree of acute inflammation was noted. The major criterion was the number of polymorphonuclear cells. This

‡The term "allergic inflammation" is used from a histopathologic, not from a clinical, point of view.

TABLE 1

NUMBER OF SENSITIZED RABBITS INJECTED INTRASINALLY WITH PNEUMOCOCCI	DEGREE OF SINUSITIS
4	Severe
5	Moderate
5	Slight
3	Negligible
2	Absent

TABLE 2

NUMBER OF CONTROL RABBITS INJECTED INTRASINALLY WITH PNEUMOCOCCI	DEGREE OF SINUSITIS
3	Severe
3	Moderate
6	Slight
3	Negligible
1	Absent

was graded as severe, moderate, slight, negligible or absent. There was agreement in the independent estimates of the two individuals. The results are seen in Tables 1 and 2.

It is obvious that the degree of acute inflammation was just about similar in the sensitized and the normal sinuses.

DISCUSSION

It may be argued that the sensitization produced by the repeated injections of egg white is not comparable to that which occurs in the allergic individual. However, the histological results are strikingly similar. Eosinophiles are numerous, along with cells of chronic inflammation and some polymorphonuclear leucocytes in the sensitized membranes. Goblet cells are also present. The membranes are often thickened and edematous, and show increased numbers of connective tissue cells.

Others may contend that the sinus inflammation is not allergic, but is the result of the foreign material present in the lumen. Foreign

matter such as agar will, it is true, produce an inflammation of the sinus membrane, although less in degree than the egg white and agar. However, we have previously shown[6] that the adjacent oral mucous membrane is hypersensitive to injection of 0.1 cc. of egg albumen solution. Therefore, it is likely that the lining mucosa of the sinus which has been the repeated site of contact with the specific sensitizing stimulant is equally hypersensitive, if not more so. Therefore, although the sinus inflammation may be partially the result of nonspecific irritation of the organ, the reaction is undoubtedly largely allergic because of the specific effect of repeated injections of the sensitizing egg white.

These experiments would seem to bear out those clinicians who note no difference between allergic and normal individuals in susceptibility to pathogenic organisms. However, one must be cautious in applying the results of these relatively simple experimental procedures to the complicated problem of the allergic diathesis.

CONCLUSIONS

Virulent pneumococci were introduced into the sinuses of rabbits which had been previously sensitized to egg albumen by means of repeated injections into the sinuses and also into the sinuses of normal controls. Histological examination disclosed similarity in the degrees of inflammation in the two groups.

104 S. Michigan Avenue

REFERENCES

1. Vaughn, W. T., and Derbes, V. J.: A Comparative Study of the Incidence of Acute Infectious Diseases in Allergic and Nonallergic Persons, J. All. 12:477, 1941.

2. Duke, W. W.: Allergy, Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction, St. Louis, C. V. Mosby Co., 1925, p. 68.

3. Rackeman, F. M., and Colmes, A.: Studies in Asthma V. The Clinical Characteristics of Hypersensitiveness, J. All. 1:2, 1929.

4. Feinberg, S. M.: Allergy in General Practice, Philadelphia, Lea and Febiger, 1934, p. 46.

5. Cannon, P. R., and Hartley, G., Jr.: The Failure of Allergic Inflammation to Protect Rabbits Against Infection with Virulent Pneumococci, Am. J. Path. 14:87, 1938.

6. Frank, I., Blahd, M., and Howell, K.: Experimental Hypersensitivity of Mucous Membranes of the Upper Respiratory Tract, Arch. Otolaryng. 35:918, 1942.

VIII

X-RAY TREATMENT OF DISEASES OF THE LARYNX*†

MAURICE LENZ, M.D.

NEW YORK

The treatment of diseases of the larynx with x-rays is predicated on the supposition that the pathologic tissues are more sensitive to the inhibiting influence of x-rays than the adjacent normal tissues, as both are exposed to the same damaging effects. Radiosensitivity, however, is not synonymous with radiocurability, as for example, when a radiosensitive diseased process is too extensive to be curable by irradiation.

X-ray treatment is employed chiefly in three groups of diseases of the larynx. These are chronic inflammation, benign tumors and cancer.

Inflammatory tissue is more sensitive to x-rays than the adjacent normal tissue, and the latter remains practically unaffected by the small x-ray doses necessary to inhibit the growth of the former. These small doses are usually repeated at weekly intervals or more often until satisfactory regression of the inflammatory infiltrate has been accomplished. This regression is accompanied by a gradual disappearance of bacteria from the granulation tissue, in spite of the fact that ordinary therapeutic doses of x-rays are inadequate for direct bactericidal action.

Benign tumors do not respond to x-ray therapy as readily as inflammatory tissue and some are so radioresistant as to make their treatment by x-rays impractical.

The treatment may be successful in hemangiomas and papillomas, whereas surgical removal is preferable in myxomas, fibromas and chondromas.

Carcinoma of the larynx is usually more radioresistant than either of the first two groups. The x-ray dosage which is required

*From the Department of Radiotherapy of the Presbyterian Hospital, New York.

†Presented before the American Laryngological Association, Atlantic City, N. J., May 26, 1942.

to arrest the growth in most of these cases is close to the maximum tolerated by the normal tissues and produces sloughing of the irradiated epidermis, the laryngeal and the pharyngeal mucosa. Unless the dosage has been too intensive, healing follows soon after the slough has separated, leaving little or no clinical evidence of radiation damage of the normal tissues. A careful study of tissue changes in cases irradiated at the Presbyterian Hospital and elsewhere was undertaken by G. R. Brighton, Franz Altmann and Cornelius Hagan, Jr., of our laryngological staff.[2] In cases which clinically do not show any radiation changes, there may be hyaline degeneration of the irradiated connective tissue fibers and proliferation of the endothelium of the capillaries and smaller veins, with consequent reduction in vascularization. The inherent radiation damage may not manifest itself clinically unless the tissues are again irradiated or are exposed to trauma; they may then undergo necrosis, especially as they have little resistance to infection, which is always present in the larynx. Because of the danger of injury, x-ray treatment of cancer of the larynx is not repeated except in rare instances. On two occasions, the larynx has been exposed to two full courses of x-ray treatment four months apart, without clinical evidence of damage. This procedure is not recommended under ordinary circumstances.

X-RAY THERAPY OF INFLAMMATION OF THE LARYNX

Acute laryngitis may react favorably to treatment by x-rays, but is not used. It is usually self-limited and otherwise can be controlled more readily by other means such as vocal rest and local medications.

X-ray treatment of chronic laryngitis is also attempted rarely. Though the rays do not attack the causative agent, producing the inflammatory reaction, regression of the granulation tissue can be expected after moderate x-ray dosage.

Pachydermia of the larynx should also react favorably.

Leukoplakia requires large dosage and may recur after it has disappeared, as the x-rays do not attack the cause of the disease. The possibility of overlooking a silent carcinoma amid the patches of leukoplakia should be borne in mind, even if several biopsies have failed to reveal cancer.

The inflammatory diseases of the larynx in which x-ray treatment has been carried out most often are: tuberculosis, blastomycosis and scleroma.

Tuberculosis of the Larynx. Though x-ray therapy of laryngeal tuberculosis has been popular in central Europe for fifteen years, it has not been generally accepted in the United States. Tonsey[38] (1904), Harland[15] (1906) and Turner[39] (1907) were among the first to attempt this treatment. The value of x-ray treatment in experimentally produced laryngeal tuberculosis in guinea pigs was tested by Brunings and Albrecht[4] in 1920. After a laryngotomy the split larynx was spread open; one side was protected from the x-rays by a lead shield, while the other side was exposed to the rays. The tuberculosis healed only on the side exposed to x-rays. Supportive clinical evidence of the value of x-ray treatment was produced by Rickmann[34] in 1924. While working in a tuberculosis sanitarium, Rickmann compared the results of treatment of laryngeal tuberculosis in two groups of patients—a group composed of 266 patients, who received routine sanitarium treatment, and another group composed of 745 patients, who had, in addition to the routine care, x-ray treatment to the larynx. A difference of 24 per cent in improvement resulted in favor of the second group of patients, which Rickmann attributed to treatment with x-ray.

Benefits from x-ray therapy in laryngeal tuberculosis are claimed chiefly in the chronic productive type, and the treatment is said to be contraindicated in the more rapidly progressive, exudative type with marked edema and ulceration. The productive type, however, has a natural tendency to heal without the aid of x-ray therapy, and it is therefore difficult to estimate the value of the addition of this treatment.

Prognosis of the laryngeal process is influenced by the status of the accompanying pulmonary disease. Collapse therapy and rest in bed are often sufficient to effect a cure of the laryngeal disease, provided that vocal rest is also maintained. Thus, Myerson[29] reported healing laryngeal tuberculosis in 87 of 145 patients who had no direct treatment to the larynx.

The x-ray dosage which is recommended for laryngeal tuberculosis is generally low. Zange[41] stated that about 60 r (10 per cent E.D.) may produce breaking down in the progressive exudative type, but believes that the productive type will tolerate up to 600 r (100 per cent E.D.) given in one sitting. We prefer much lower dosage than this as the danger of aggravating the disease with larger doses is too great. We therefore start with 5 to 25 r to each lateral 6 x 8 cm. laryngeal field (200 kv., 0.5 mm. Cu, 50 cm. T.S.D. or 130 kv. and 3 or 4 mm. Al) once weekly, under careful clinical

supervision. Depending upon the local and general reaction, this dosage may be repeated six to twelve times. Our experience with x-ray treatment of laryngeal tuberculosis has been too limited to permit fair and critical judgment. Further trial may be justified, but should be carried out preferably in sanitaria, in which the relative importance of other treatment can be evaluated accurately.

Blastomycosis. X-ray therapy of this rare disease is usually combined with large doses of iodides. It should be differentiated from tuberculosis with which it is frequently confounded. Improvement by x-ray therapy after failure of the usual means, such as iodides and tartar emetic has been reported.[5] The danger of breaking down the lesion by x-ray therapy is less than in tuberculosis. However, the disease forms small abscesses and large doses may tend to increase necrosis. Repetition and the amount of the x-ray dose is governed by the reaction to the treatment. The dose is somewhat larger than in laryngeal tuberculosis, and 50 r to each side of the larynx once a week with 200 kv., 0.5 mm. Cu or 130 kv. and 3 mm. Al is usually administered.

Scleroma. Scleroma is rarely limited to the larynx and is usually associated with similar lesions in the nares and the nasopharynx; from here the disease spreads insidiously towards the larynx along contiguous mucous membranes. A comprehensive review of the clinical course of the disease was given by Figi and Thompson[11] in 1925.

As the disease is usually too extensive, when first seen, to permit total excision, surgery should not be done except for purposes of biopsy or as an emergency measure. Microscopically this organized granulation tissue often contains foam cells (Mikulicz), hyaline degeneration bodies (Russell) and many eosinophiles.[10]

Since 1902, when Gottstein[14] successfully treated a case of scleroma with x-rays, various authors have reported marked benefit from the therapeutic use of x-rays. The granulation tissue regresses readily under this treatment. The clinically inappreciable extensiveness of the process, however, may lead to the use of radiation fields which are inadequate and account for the fact that permanent cures are more rare than temporary improvement. At the meeting of the American Radium Society in June, 1942, Guillermo Montano Islas and Louis Vargas y Vargas, of Mexico City, reported the results of x-ray therapy in 72 cases of rhinoscleroma treated during the preceding 18 months. They used 220

kv., 15 ma., 50 cm. T.S.D., 0.5 mm. Cu plus 1 mm. Al, and treated the laryngeal disease through one anterior 6 x 8 cm. portal. In cases also involving the nose and the nasopharynx they used a separate 7 x 7 cm. square portal over an anterior nasal field with lead goggles over the eyes. In the laryngeal cases they started with 50 to 80 r daily gradually raising the dosage to 150 or 200 r. Ten days or two weeks following the first treatment they noted reduction in the mechanical difficulties of breathing and beginning regression of the granulation tissue. In only 10 per cent of the cases, however, was a single series of treatments; that is, a total of 1500 or 2000 r in two weeks, sufficient to produce complete disappearance of the disease. In 60 per cent of the patients a second series of treatments was necessary and in 30 per cent three to four series had to be given.

Recently, Dr. Schwartz and I had occasion to re-examine a patient whom we had treated with x-rays ten years previously for a rhinoscleroma of the nares, pharynx and larynx. Dr. Schwartz[35] had reported the case in 1935. All evidence of active disease had disappeared. The nares and nasopharynx appeared fairly normal; the chink of the glottis, however, had remained markedly narrowed and the patient still breathed through a tracheotomy opening. Shortly before the x-ray therapy the patient had obtained immediate, though temporary, relief, when Dr. Imperatori excised an obstructing laryngeal mass and a shelf, through the direct laryngoscope. Another patient, with a similarly extensive scleroma, treated ten years ago, also appeared clinically cured when last seen by Dr. Schwartz five years ago. We gave 75 to 100 r to each right and left, 6 x 8 cm., lateral laryngeal field, either daily, or every two or three days, depending upon the appearance of the laryngeal reaction. The total dose to each of these two fields was carried up to 1000 or 1500 r with 200 kv., 0.5 mm. Cu filter and 50 cm. T.S.D.

In planning x-ray treatment of laryngeal scleroma it is important not to limit the treatment to the larynx, but also to include the other portions of the nose and throat which have been involved.

X-RAY THERAPY OF BENIGN TUMORS OF THE LARYNX

X-ray treatment of benign tumors of the larynx has been successful chiefly in a few hemangiomas and various types of papilloma, though other benign tumors have also been treated.

Hemangioma. Radium in external packs or applied intralaryngeally has been used more extensively[36] than x-ray therapy. Levbarg

is quoted by Moore[30] as having used x-ray therapy successfully. Moore also mentions Hoffman who found that a dose of 400 r in three exposures at four-day intervals resulted in improvement for sixteen days, with subsequent return of dyspnea, requiring tracheotomy. In other parts of the body, port wine marks are notoriously radioresistant and cavernous hemangiomas in infants respond more readily than those in adults. Attempts to treat hemangiomas of the larynx with x-rays should therefore be limited to the cavernous variety. Treatment may be more successful if the patient is very young, but should not be given unless the hemangioma is causing, or is likely to cause, symptoms. Preliminary tracheotomy may be indicated to avoid asphyxia if the hemangioma is likely to swell as a result of the radiation. The danger of this complication may be reduced if small doses of fractionated x-ray therapy are given under careful daily laryngoscopic control. The following case successfully treated in the Radiotherapy Department of the Presbyterian Hospital is illustrative of the dosage used.

CASE 1.—H. E., a baby girl, eight months old, had a tracheotomy done at the age of three months because of laryngeal obstruction. The diagnosis of hemangioma was corroborated by biopsy of a specimen from the larynx at the age of seven months. From June 9 to June 25, 1941, 1000 r with 200 kv., 25 ma., 50 cm. T.S.D., 0.5 mm. Cu plus 1 mm. Al were administered to each side of the larynx with a 5 cm. cone; 150 r were given daily to alternating laryngeal fields. The tracheotomy tube was removed two months after starting the treatment and a follow-up examination on May 11, 1942, showed no evidence of disease.

Papilloma of the Larynx. According to Koch[21] richly cellular papillomas, with a stroma of dense connective tissue and poor in blood vessels, are more radiosensitive than papillomas poor in cells, with loose connective tissue stroma, though rich in blood vessels. In practice, indications for x-ray treatment of papillomas vary with the clinical type. Papillomas occur in children or in adults and may be single or multiple.

Single papillomas are uncommon and usually occur in adults. Of 194 papillomas reported by New and Erich,[32] 28 were single, and were all found in adults. These papillomas should not be treated by x-rays. They are not very radiosensitive, high x-ray dosage being required to arrest their growth. It is simpler to remove them surgically.

The need for x-ray treatment of multiple papillomas in children has been reduced to a minimum as they are now effectively treated by estrogen therapy, as shown by Broyles.[3] However, Foster,[12, 13] who has had considerable experience with low voltage x-ray ther-

apy states that he has seen excellent results from this treatment if given in adequate amounts over a period of three months. The technique which in his experience has given satisfactory results has been 100 kv., 5 ma., filter 4 mm. Al, T.S.D. 40 to 45 cm., sixteen treatments, one every five days, five to fifteen minutes each, or a total dosage of about 3500 to 4000 r. Solomon and Blondeau[37] claim as good results from treatment with higher voltages. New[31] prefers the use of intralaryngeal radium by means of a Lynch suspension apparatus followed by a radium pack over the larynx. Crowe and Breitstein[8] also prefer the same method. In our limited experience with 200 kv. (0.5 mm. Cu plus 1 mm. Al, 50 cm. T.S.D.) the dosage usually required is about 2000 r to each of two lateral laryngeal fields 6 x 8 or 7 cm. circular fields large enough to include the larynx, and given in a period of a few weeks.

In multiple papillomas of adults, treatment by x-rays at times succeeds after the failure of conservative surgery, as illustrated in the case quoted below. It can therefore be used occasionally, in place of radical excision of the mucosa.

CASE 2.—Female, aged 22 years, was admitted to Presbyterian Hospital on March 2, 1937, for excision of multiple papillomas of the left cord, anterior commissure and ventricle, the right cord and subglottis. Five unsuccessful attempts were made on March 3, March 24, April 21, July 7 and August 11 to remove the papillomas by biting forceps. In view of the failure of this method to prevent recurrences, it was decided to try x-ray treatment, and from August 23 to September 17, 1937, a left and right 6 x 8 cm. lateral laryngeal field was exposed to 20 daily treatments. The technical factors were: 200 kv., 25 ma., 1 mm. Cu plus 1 mm. Al T.S.D. 50 cm. During this period each of the two fields received 100 r daily, or a total dose of 2000 r. The papillomas disappeared promptly and were not seen again on laryngeal examination from October, 1937, to January 14, 1941. At this time a single small papilloma was noted below the middle of the right cord. This has now been observed for a year without any treatment and has not changed in size. No other papillomas have developed.

Follow-up studies on several other similar cases, some without preceding surgery, except for biopsy, suggest that x-ray treatment of multiple papillomata in adults is worthwhile. About 2000 r to each right and left lateral laryngeal field, as given in the case quoted above, is the dosage generally required.

CANCER OF THE LARYNX

In the early days of x-ray therapy of cancer of the larynx[20, 26] before the importance of the technical details of the treatment was fully appreciated, it often occurred that the amount of x-ray which was administered was too large and that the period of treatment was

too short. This excessive dosage resulted in necrosis of the laryngeal cartilages and brought the treatment into disrepute.

As shown by our own experience, it took a long time to overcome this lack of confidence. During the five years between 1926 and 1931, when we treated the first cases at Montefiore Hospital and at the Presbyterian Hospital, only 14 patients with cancer of the larynx were referred to us for this treatment. During the next four years, between 1932 and 1936, after the late Dr. Coakley became convinced of the value of this therapy, we began to have earlier, more curable cases of cancer of the larynx and treated 89 patients. At present, the treatment of most of the cases of laryngeal cancer admitted to the service of Dr. Kernan at the Presbyterian Hospital is decided upon after a consultation between members of the laryngological and radiotherapeutic services. A joint follow-up clinic meets once a month in the department of radiotherapy. In the clinic, members of both departments have an opportunity to familiarize themselves with the advantages and disadvantages of surgical and x-ray treatment.

The administration of cancericidal x-ray doses without seriously damaging the adjacent normal tissues is a difficult problem. In 1919, Coutard,[6, 7] at the suggestion of Regaud, started to divide the large total amount of x-rays needed to arrest the growth of cancer of the larynx into a number of small daily treatments. This series of x-ray exposures took several weeks and was not repeated. The fact that the entire treatment was completed before radiation changes had lowered the tolerance of the surrounding normal tissues permitted the administration of the required dose without excessive damage to the normal tissues. In so-called "second x-ray series" or x-ray treatment after preceding radium therapy, the tolerance of the connective and the vascular tissues has already been lowered by the damaging effects of the first irradiation treatment. The tolerance of the cancer on the other hand is not reduced to the same degree, as the injured cancer cells have been largely replaced by new cells through division of a few cancer cells which escaped radiation damage.

Present Technique of X-ray Treatment. The technique of x-ray treatment of cancer of the larynx initiated by Coutard has varied during the past 22 years, especially as to the period during which the treatment is given and the amount which is administered daily. Coutard, whose x-ray machines delivered only 4 ma., thought it important that the daily treatment be protracted over

a period of two or more hours. In 1928 when the Montefiore Hospital, New York, purchased an x-ray therapy machine which delivered 30 ma., I had the opportunity of administering the same daily dose in fifteen to twenty minutes instead of several hours. The first patients with various types of cancer treated by this technique were presented at the meeting of the New York Roentgen Ray Society, on May 18, 1931, and the first report of x-ray treatment of laryngeal cancer with 30 ma. was published in the Journal of the American Medical Association (November, 1932).[21] In the Radiotherapy Department of the Presbyterian Hospital, the treatment is carried out under daily laryngoscopic control by the resident radiotherapists. The technical factors used are 200 kv., 25 ma., 1 to 2 mm. Cu or Thoreus filter, plus 1 mm. Al, and a 6 x 8 or a 7 cm. circular field over each lateral surface of the larynx. Occasionally smaller or larger fields are used and rarely an anterior or posterior field is added, depending on the location and extent of the disease. Treatment is started with about 50 to 75 r to each side of the larynx. After a few days and depending on the laryngeal reaction, this is raised to 100 or 125 r per field. The treatment is continued for four to seven weeks up to a total of about 3000 to 3500 r to each side, depending upon the size of the field and the laryngeal reaction. At the height of the reaction, the epithelium of the irradiated mucosa sloughs off and the defect is covered by a pseudodiphtheritic membrane. Similar membranes may appear several times during the course of treatment but should be most marked at the end of the treatment. When a membrane appears before the series of irradiations have been completed, treatment is either discontinued for several days, or the daily dosage is reduced to 50 r per field. The treatment is resumed when the membrane has started to regress and the daily dosage is gradually raised back to 100 or 125 r per field. An early membrane may often become noticeable about the twelfth or fourteenth day of treatment, depending upon the size of the field and the daily dosage. Failure to obtain even a slight pseudodiphtheritic membrane before the end of the treatment may indicate inadequate dosage. Nevertheless, two patients, one treated five and the other ten years ago, who did not develop a pseudodiphtheritic membrane, are now clinically free from cancer. An early pseudodiphtheritic membrane limited to the growth usually denotes a radiosensitive tumor. Edema of the arytenoids appearing early in the series of treatments indicates that the daily dosage is too high and should be reduced. This is often seen with fields which are 8 x 10 cm. or larger, with technical factors outlined above, after 750 r or more have been administered to each side of the larynx.

Patients do not tolerate high total doses over large neck fields, as the immediate reaction and late sequelae are too severe. The acute pharyngitis and the consequent dysphagia which appear near the end of the treatment make drinking painful and may lead to dehydration. At times hospitalization is desirable during the height of reaction, which usually follows soon after the termination of the treatment. Hospitalization permits more efficient control of the patient's fluid intake; drinking may be insisted upon; gavage, proctoclysis, hypodermoclysis and venoclysis may be carried out more easily. Such complications as aspiration pneumonia have been rare in those patients who have had hospital care during this period. Since we have avoided severe reactions and varied the daily dosage in accordance with the laryngoscopic appearance of the mucosa and arytenoids, the number of complications have been markedly reduced.

X-ray treatment of cervical lymph node metastasis from cancer of the larynx is applicable chiefly to two groups of cases: one, where only temporary growth restraint and palliation of pain are indicated, because of the advanced stage of the cancer, and the other where the original cancer is known to be radiosensitive and it is assumed that the metastases will react in a similar way. An example of such a radiosensitive cancer would be a fungating growth of the epiglottis. On the other hand, cervical lymph nodes, which are likely to be more radioresistant, for example, those secondary to cancer of the cords, are preferably treated by radical neck dissection or by implantation of radium or radon.

While nearly all malignant tumors of the larynx arise from the epithelium of the laryngeal mucosa and are epitheliomas, occasional lymphosarcomas and fibrosarcomas are encountered.

Lymphosarcoma. This rare laryngeal tumor usually forms a part of a generalized process as in the case of Cummings.[9] The tumor is radiosensitive and x-ray dosage is somewhat less than that used for carcinoma of the larynx. Prognosis and x-ray dosage are governed not only by the local regression, but by the extent of the lymphosarcoma when beginning treatment, especially as to whether the process has generalized or is still localized and accessible to vigorous x-ray dosage.

Fibrosarcoma. Fibrosarcoma of the larynx is seen rarely. It is very radioresistant and should be treated surgically. In a case not included in this series, a postoperatively recurring fibrosarcoma arising in the neighborhood of the arytenoid grew rapidly during the

several weeks which it took to administer 3000 r to each side of the larynx. It caused the patient's death shortly thereafter.

CARCINOMA OF THE LARYNX

Personal Clinical Material. In an effort to clarify somewhat the indications and contraindications for x-ray therapy in carcinoma of the larynx, a study was made in January, 1942, of the clinical histories of 89 patients treated at the Presbyterian Hospital from 1932 to 1936. In 14 patients x-ray treatment had been given after total laryngectomy, in 5 this had been done after partial laryngectomy, and 70 patients had been treated only by x-ray. The relative proportion of patients now clinically free from cancer for over five years after x-ray treatment may be seen in Table 1:

TABLE 1.—X-RAY TREATMENT OF CANCER OF THE LARYNX
PRESBYTERIAN HOSPITAL, 1932-1936

Type of treatment	No. treated	No. clinically free from cancer, January, 1942
X-ray treatment after total laryngectomy	14	4 (9 years)
X-ray treatment after partial laryngectomy	5	3
X-ray treatment only	70	13
Totals	89	20

X-ray Treatment After Total Laryngectomy. In 3 of the 4 patients treated after total laryngectomy, who have now been clinically free from cancer for over nine years, microscopic examination of the laryngectomy specimen showed cancer along the line of excision. In other words, if they had not had postoperative x-ray treatment, these operated cases surely would have had a local recurrence. While this number of cases is small, we regard it as adequate proof of the value of postoperative x-ray treatment in cases in which the entire cancer has not been removed surgically. With the cartilage entirely excised, there is no danger of radiochondronecrosis, and adequate dosage may be administered without fear of this complication.

X-ray Treatment After Partial Laryngectomy. Among the 5 patients treated with partial laryngectomy, 3 patients are now clinically free from cancer. This may have been due to the x-ray

treatment, but there is no microscopic support for this belief, such as was available in the cases after total laryngectomy. One of the patients died of a radionecrosis of the larynx. This is a complication which is not infrequent if x-ray treatment is given after a partial laryngectomy, as the laryngeal cartilage remaining after partial removal does not withstand severe x-ray dosage. If x-ray treatment is to be given after laryngectomy, it is better to remove all the cartilage either by decortication or by total laryngectomy than to excise part of it.

Preoperative X-ray Treatment. In cases in which it is difficult to decide whether to choose surgery or x-ray therapy, a preoperative course of x-ray treatment may be given to test the radioresponsiveness of the cancer. If there is definite regression of the tumor after one-half or two-thirds of the full dose has been administered, x-ray therapy may be continued, otherwise an immediate laryngectomy should be performed. We have been trying preoperative x-ray therapy for only a few years, and as yet are not prepared to support this statistically.

Laryngectomy After X-ray Therapy. Healing is not interfered with materially if laryngectomy is done after a full course of modern fractionated x-ray treatment. In a patient in whom we had failed to arrest a cancer of the cord with 3000 r, fields 6 x 8 cm. to each side of the larynx, Dr. Imperatori did a laryngectomy four months later. Postoperative healing was delayed perhaps for a week, but a perfect scar resulted and the patient has now remained well for six years.

Tracheotomy. If tracheotomy is indicated it should be done low in the neck so as to keep the cut edges of the cartilage out of the field of radiation, as the resistance to x-rays of this surgically damaged cartilage is distinctly lowered. The need for tracheotomy before or during x-ray treatment occurs when the disease is extensive. Tracheotomy after this treatment is usually done because of a complicating postradiation edema of the larynx followed by radionecrosis of the cartilage. This often results in the death of the patient. In a previously reported series of 42 patients[22] in whom a tracheotomy had been performed before, during or after x-ray treatment, only 2 patients remained clinically free from cancer.

Recurrence of cancer in the tracheotomy opening has not responded well to treatment with x-rays. None of the patients treated by us for this complication was benefited for more than a few months.

Cases of carcinoma of the larynx treated by a combination of surgery and x-ray therapy do not lend themselves to evaluation of either therapy as readily as those cases in which only one form of treatment has been carried out. A more careful study was made of the 70 cases treated only by x-ray therapy. On the basis of these cases, radiocurability was investigated as to its relationship to the various characteristics of cancer such as the microscopic structure, the location, extent and tendency to invade the adjacent tissues.

Three of the patients treated in 1932 and 1 treated in 1935 who are now clinically free from cancer were presented at the meeting of the American Laryngological Association in June, 1942. The technique in the 3 cases treated in 1932 consisted of daily x-ray treatment to one of two lateral laryngeal fields, 400 r per field, up to the desired total quoted below: 200 kv., 8 ma., 2 mm. Cu plus 1 mm. Al, 50 cm. T.S.D. In the fourth case we used 200 kv., 25 ma., 80 cm. T.S.D., 2 mm. Cu plus 1 mm. Al and 200 r daily to alternate lateral laryngeal fields.

CASE 3.—C. R., male, 60 years of age, had a poorly differentiated epidermoid epithelioma involving the middle third of the left vocal cord, and a slightly fixed left arytenoid; this fixation was considered inflammatory and disappeared promptly. Cervical lymph nodes could not be palpated. The patient was given 3200 r to each a right and left lateral laryngeal 6 x 8 cm. field in nineteen days beginning October 6, 1932.

Comment. This case and the following one are the only cord cancers which microscopically were not well differentiated. The patient is now free from clinical evidence of cancer, but has slight telangiectasia over the treated area.

CASE 4.—L. R., male, 51 years of age, had a poorly differentiated epidermoid epithelioma involving the anterior half of the right vocal cord with extension to the anterior commissure. The cervical lymph nodes were not clinically enlarged. From August 24 to October 1, 1932, he was given 4800 r over a right lateral laryngeal field of 4 x 5 cm. and 4600 r over a 6 x 8 cm. left laryngeal field. Seven months after irradiation a persisting thickening of the cord caused Dr. Coakley to take a biopsy which microscopically revealed only laryngitis. A slight thickening of the cord has persisted since then and the laryngeal mucosa as well as the skin shows slight atrophy and telangiectasia. The patient's voice usually sounds normal, but he becomes hoarse when he is in a room where there is smoke, or when he develops a cold.

Comment. This patient received more irradiation than we have given others. At the time when he was treated, the x-ray dosage was not as standardized as it is at present.

CASE 5.—J. D., male, 46 years of age, had a well-differentiated squamous epithelioma involving the anterior surface of the epiglottis, extending to the right aryepiglottic fold and the right arytenoid, and a clinically metastatic 2 cm. node, near the bifurcation of the right carotid artery. Treatment was for 27 days begin-

ning November 15, 1932, to December 12, 1932, 3200 r over a right laryngeal 10 x 10 cm. field, 2600 r over a left laryngeal 6 x 8 cm. field and 2400 r over a posterior 6 x 8 cm. field.

Comment. This case was a moderately differentiated, extensive but fungating epiglottic cancer with clinically metastatic lymph nodes, which in spite of its extensiveness was controlled by x-ray therapy.

CASE 6.—N. W., male, 34 years of age, had a large fungating undifferentiated epithelioma of the left band with edema of the left arytenoid, a 2 cm. clinically metastatic lymph node in the left carotid region, and a 1 cm. firm lymph node behind the right angle of the mandible. From January 29, 1935, to March 19, 1935, daily x-ray treatments, 200 r, were given alternately to a left and right lateral laryngeal field, 8 x 10 cm., up to a total of 4200 r on the left and 3600 r on the right. The mass promptly disappeared but from the beginning of April, 1935, to the end of 1936 there persisted edema of both arytenoids and permanent fixation and deformity of the left arytenoid where it had been destroyed and scarified by the carcinoma. The late Dr. Buckley and I did not think that the patient's cancer had been destroyed. Time and again we thought that a biopsy was indicated and that a laryngectomy would have to be done. The only reason for delaying the biopsy was the fear of starting a radiochondronecrosis. The edema of both arytenoids gradually lessened and now there is none left. As the years passed by, it became clear that this edema had been due to overirradiation and not to cancer. At present, seven years after treatment, the patient shows no evidence of cancer.

Prognosis and Microscopic Classification. Microscopic classification of carcinoma of the larynx by itself is no longer regarded as a reliable guide either to radiosensitivity or to radiocurability of the process. Coutard has frequently stated that he considered the mobility and lack of infiltration of tumor the most important signs of radiosensitivity and, within certain limits, of radiocurability of cancer of the larynx. Cutler[10] has supported this view and emphasizes that radiosensitivity of cancer of the larynx cannot be determined on the basis of microscopic structure. Harris and Klemperer[17] were among the first to question the importance of the microscopic structure in determining the outcome of x-ray treatment in cancer of the larynx.

Our impression is that by itself microscopic classification has little prognostic significance. It may be of some help, however, if the more important clinical data, such as the extent and infiltrative tendencies of the cancer, are also taken into account. Our clinical material which has been referred to us from various outside sources does not lend itself to accurate evaluation of the importance of microscopic classification. Of the 70 cases, Dr. A. P. Stout, surgical pathologist of the Presbyterian Hospital, was able to classify only 42 cases. Slides of the remainder were either not available at the time of the classification or could not be fitted

into one of the three groups postulated by Dr. Stout. All of the clinically cured cases except 1 were proven microscopically, though 3 were classified only as carcinoma, for reasons as above. Of the 42 cases, 7 were classified as well differentiated, with only 1 clinically cured case; 10 were labelled poorly differentiated with 4 clinically cured; 25 were placed in the group of medium differentiation and 2 of these were clinically cured.

The factors which appeared to be of far greater prognostic importance than the microscopic structure were the location, extent and infiltrative tendency of the cancer.

Location. The primary site of laryngeal cancer is easily discernible in cases in which the lesion is early and small. In extensive involvement, the primary site may be recognized if the growth is observed while it is regressing under the influence of x-ray therapy: according to Coutard, the primary lesion is usually the last one to clear up. The influence of the location of the primary tumor on prognosis may been seen in Table 2. In this, 70 patients treated only by x-ray were classified according to the assumed site of origin.

TABLE 2.—TREATMENT ONLY BY X-RAYS—LOCATION AND RESULT

Assumed primary site	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Vocal cord	24	5	19
Band	6	2*	4
Subglottis	2	0	2
Epiglottis	15	4*	11*
Aryepiglottic fold	2	1*	1
Arytenoid	18	0	18*
Pyriform	3	1*	2
Totals	70	13	57

*Clinically metastatic lymph nodes except in 2 cured cases of cancer of the epiglottis.

The variation in the outcome of treatment according to the location of the cancer is related to differences in lymphatic drainage, which influences local extensiveness and regional metastasis, and to the occurrence of inadequately drained foci of infection, for example, in the region of the arytenoid cartilages.

Local Extent of Cancer of the Cords. The relation between local extensiveness on admission and outcome of x-ray treatment is illustrated in Table 3. In this table, patients with cancer of the cord were separated into two groups: those with the disease limited to one cord and the others in which it had extended beyond the cords.

TABLE 3.—CANCER OF THE VOCAL CORDS—EXTENT ON ADMISSION AND RESULT

	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Limited to one cord	5	3	2
Also involving other laryngeal structures	19	2	17

Of the 2 patients classified as dead, among those with cancer limited to one cord, 1 was lost sight of, free from clinical evidence of cancer three and a half years after treatment. In the other, the cancer arose on the posterior half of the true cord, where silent extension to the arytenoid may have easily occurred. The gravity of involvement of the arytenoid in cordal cancer will be commented on later. Of the 17 patients who died and who had involvement of other structures before treatment, 1 died of heart disease free from cancer and 1 developed radionecrosis of the laryngeal cartilages without clinical evidence of cancer.

There can be no doubt that the extent of the cancer on admission in this small group of cases definitely influenced the results of treatment by x-rays.

Cancer of the Arytenoids. Invasion of the arytenoids by cancer, whether this is an extension from a primary site on the mucosa covering the arytenoids or is a spread from a cancer of the cord, often signifies that the cancer is incurable by treatment with x-rays. Inflammatory fixation of the arytenoids usually clears up promptly under x-ray therapy and it is not included in this discussion. Kramer[22] reported a small series of patients with laryngeal cancer with fixed arytenoids presumably invaded by cancer in whom the results of x-ray therapy were satisfactory. We also have a number of patients treated by x-ray who are now free from cancer, who had, and still have, fixed arytenoids. As seen in Tables 2 and 4, however, all patients with fixed arytenoids secondary to

cancer presumably originating on the cord or arytenoid mucosa in the present series were dead when we reviewed our material. Invasion of the arytenoids appeared less serious when it represented extension from primary sites on the band, epiglottis, aryepiglottic fold and pyriform sinus; several of these patients who had fixed arytenoids are now clinically free from cancer.

Three factors contribute to the gravity of invasion of the arytenoids by cancer. Contrary to cancer on the free edge of the cords in which hoarseness often brings about an early diagnosis, cancer of the arytenoids at first may be silent and is usually extensive before it is recognized. A rich lymphatic network covering the arytenoids contributes to the frequency of metastasis to the cervical lymph nodes and to the fact that these are usually involved before treatment is started. As seen in Table 2, clinically metastatic lymph nodes on admission were found in every case, presumably arising in the arytenoid region. The arytenoid cartilages are located in a sort of pouch to one side of the tracheal air column, expelled in coughing. Coughing therefore cannot help to empty this cavity if necrosis of the arytenoids occurs due to invasion by cancer and by bacteria. Drainage is uphill and inadequate. The slough cannot be expectorated and remains at the bottom of the depression. The infection persists and readily spreads laterally. Necrosis, especially of the cartilages, continues and occasionally may be made worse by the large x-ray doses given in order to cure the cancer.

The seriousness of the involvement of the arytenoids in cancer of the cords may be gleaned from Table 4.

TABLE 4.—CANCER OF THE VOCAL CORDS—FIXATION OF ARYTENOIDS AND RESULT

	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Fixing arytenoid	9	0	9
Not fixing arytenoid	15	5	10

Cancer of the Epiglottis. The influence on prognosis of the extensiveness of the cancer on admission and of its tendency to invade adjacent tissues is shown in the study of the cases of cancer of the epiglottis. Papillary, exuberating cancers which slightly invade the deeper tissues, grow mainly along the surface fungating

into the cavity of the ventricle or forward into the vallecula. In spite of their bulky appearance the primary growths and their metastases to the cervical lymph nodes usually respond readily to x-ray treatment. The reverse is true of the cancers which tend to grow inward and insidiously spread forward into the substance of the base of the tongue, as seen in Table 5.

TABLE 5.—CANCER OF THE EPIGLOTTIS—EXTENSION TO THE TONGUE AND RESULTS

	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Not invading tongue deeply	10	4	6
Invading tongue deeply	5	0	5

The discrepancy in the results obtained in cases involving the arytenoid cartilages and those involving the epiglottis is interesting (Table 2). In necrosis of the epiglottis, drainage is downward, towards the ventricle, and the necrotic material is emptied into this cavity whence it is coughed up and expectorated. Cure may result from x-ray therapy even if most of the epiglottis has been invaded by the cancer and has undergone necrosis after the x-ray treatment.

Metastases to Cervical Lymph Nodes. The bearing which metastatic involvement of the cervical lymph nodes has on survival after x-ray therapy can be seen in Table 6. Because of the paucity of lymph vessels near the free edge of the vocal cord, cervical lymph nodes are usually not involved in cord cancer unless there has been an extension to other portions of the larynx in which lymphatic drainage is richer. Those patients whose cancer on admission had already extended beyond the cord, would naturally tend to present metastatic lymph nodes more often than those in whom it is still limited to the cord.

TABLE 6.—CANCER OF THE VOCAL CORDS—METASTASIS TO CERVICAL NODES AND RESULTS

	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Clinically metastases to lymph nodes	11	0	11
Clinically no metastases	13	5	8

Cord cancer is usually a well-differentiated, slowly growing tumor giving rise to small, firm, inconspicuous lymph nodes which at first are often overlooked. These metastatic lymph nodes do not respond readily to x-rays and are preferably treated by radical neck dissection or interstitially placed radium or radon. When the nodes are fixed, or are extensive and a cure is not expected, moderate doses of x-rays may help to slow up the progress of the disease.

The presence of metastases in the cervical lymph nodes in cancer of the epiglottis is not quite as serious as in cancer of the vocal cord. In Table 7 there are recorded 4 of 13 patients with clinically metastatic nodes who were made clinically free from cancer; we have also several other similar cases in which the cancer seems to have been arrested, but which as yet have not reached the five-year period.

TABLE 7.—CANCER OF THE EPIGLOTTIS—METASTASES TO CERVICAL NODES AND RESULTS

	No. treated	No. clinically free from cancer, January, 1942	No. deaths
Clinically metastatic neck nodes	13	2	11*
Clinically no metastasis	2	2	0

*Two died, free from cancer, six years after treatment, one from pulmonary tuberculosis, the other from pneumonia.

Choice of Treatment. It is often difficult to decide whether in a particular case of cancer of the larynx it is better to perform a laryngofissure and cordectomy, a total laryngectomy or to rely upon x-ray treatment. X-ray treatment of cancer of the larynx is a serious undertaking. The reaction to it is severe and it is not tolerated by all patients.

Debilitated patients suffering from chronic infection, arteriosclerosis, advanced nephritis, cardiac disease, diabetes or chronic alcoholism may not be able to withstand the treatment and especially not the reaction which follows. The dosage is therefore often reduced and an inadequate amount administered, resulting in failure.

The number of early cord cancers recorded here is insignificant when compared to the much larger statistics of successful laryngofissures and cordectomies. There are, however, several other reports[6] of five-year freedom from cancer of the larynx after treatment with x-rays, and we also have a number of similarly obtained

clinical cures in the same type of cases treated less than five years ago. This information convinces us that the results of properly applied x-ray therapy may be as good as those of laryngofissure. Coutard[6] and Quick[33] agree with this view, whereas Martin,[28] Imperatori[18] and Jackson[19] state that all intrinsic cancers should be treated surgically. As we believe that surgery and x-ray therapy are equally efficient in these cases, we allow the patient to choose the treatment he prefers. X-ray therapy takes five to six weeks, the reactions of the mucous membrane and skin are severe and painful, but the resulting voice is better than after laryngofissure. The wound after laryngofissure heals promptly and the patient may be home in a week, but the resulting voice is husky and low-pitched. Theoretically, the curability rate with x-ray therapy should, except in the smallest easily removable cancers, be higher than after cordectomy: the zone of effective x-ray therapy includes the entire larynx, that is, clinically inappreciable extensions beyond the cord, which may escape removal if excision is limited to the cord. As yet an insufficient number of cases have been treated by x-ray therapy to permit a fair comparison, but logically it should be superior to cordectomy.

In the more extensive cord cancers the results [illegible]r x-ray therapy are correspondingly worse. Results are especi[illegible]oor if cancer has invaded the arytenoids, though a number of [illegible]ay cures have also been reported. Because of the poor results of x-ray therapy, total laryngectomy should be given full consideration in these more extensive cases.

In far-advanced cord cancer when cartilage and soft tissues have been invaded, and neither method alone is likely to be successful, total laryngectomy followed by full dosage of x-ray treatment may still save a number of patients.

Carcinoma of the band often responds readily to x-ray treatment but not infrequently recurs later. Whether x-ray or surgical treatment is preferable will depend greatly upon the local extent, and the spread to the pharynx and the cervical lymph nodes, at the time when treatment is to be started.

Cancers of the subglottis have the reputation of doing badly with x-ray therapy, yet recently, several subglottic cancers have been controlled by this treatment.

In most extrinsic cancers, the entire disease cannot be removed by laryngectomy. X-ray treatment is especially successful in the

noninvasive type of cancer of the epiglottis and its folds but does not do so well when the primary site is in the arytenoid region or in the pyriform sinus. In a few of these cases the possibility of a total laryngectomy followed by a full course of x-ray therapy should be considered. In most, x-ray treatment is preferable.

As the present discussion is concerned with x-ray therapy, treatment with radium or radon has not been considered so far. Satisfactory results were reported by Ahlbom[1] in 74 carcinomas of the larynx in which teleradium was used either as the only treatment or as a postlaryngectomy measure. Ledoux and Sluys[23] and later Harmer and Finzi[16] clinically controlled cases of laryngeal cancer by the insertion of radium needles through a window cut in the thyroid cartilage, while Quick[33] reported several remarkable cures after thyrotomy and implantation of radon seeds. Four of Martin's[27] eight cases were clinically free from cancer five years after laryngostomy and radon seed implantation. The use of intensive caustic interstitial irradiation as outlined above is not infrequently complicated by chondronecrosis of the laryngeal cartilages. The treatment is indicated only in exceptional cases in which inherent radioresistance, small size and accessibility make this method of treatment particularly suitable. In most cases, however, either x-ray therapy or surgery is preferable.

In choosing the best treatment for cancer of the larynx, the advantages and limitations of surgery and x-ray therapy and in a limited way of radium or radon therapy should be considered in each particular case. The decision is influenced by the location, the local extent, the presence of metastases, and the invasive tendency of the cancer. The best method of solving individual problems is by consultation between the laryngologist and the radiologist. A joint follow-up clinic will help to standardize criteria on which to base the choice of treatment routinely.

CONCLUSIONS

X-ray therapy is an important aid in the treatment of diseases of the larynx. The treatment is based not only upon proficiency in radiotherapeutic technique and adequate x-ray equipment, but as much upon familiarity with the local anatomy, with the natural course of the untreated disease, with the extent of the disease on admission, and the radiosensitivity of the treated normal and pathological tissues.

180 FORT WASHINGTON AVENUE

REFERENCES

1. Ahlbom, H. E.: Die Resultate der Strahlenbehandlung von Endolaryngealen Karzinomen am Radium-Hemmet, Stockholm, 1930 bis 1939; Acta radiol. 22:539, Fasc. 5-6, 1941.

2. Brighton, G. R., Altmann, Franz, and Hagan, Cornelius, Jr.: Reactions of Laryngeal Tissues Following Extended Fractional Roentgen Irradiation, Arch. Otolaryng. 33:631, 1941.

3. Broyles, E. N.: Treatment of Laryngeal Papilloma in Children, South. Med. Jour. 34:239, 1941.

4. Brunings and Albrecht: Experimentelle und kritische Untersuchungen ueber die Wirkung des Sonnenlichtes, der Roentgenstrahlen und des Quecksilberdampf-Lichtes auf die Kehlkopftuberkulose des Kaninchens, Ztschr. f. Ohrenh. 60:350, 1910.

5. Clerf, L. H., and Bucher, C. J.: Blastomycosis of the Larynx, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 45:913, 1936.

6. Coutard, H.: Present Conception of the Treatment of Cancer of the Larynx, Radiology 34:136, 1940.

7. Coutard, H., and Hautant, A.: Resultats du traitement du cancer du larynx par les rayons x, Jour. radiol. et d'electrol. 7:541, 1923.

8. Crowe, S. J., and Breitstein, M. L.: Papilloma of the Larynx in Children, Arch Surg 4:275, 1922.

9. Cummings, G. O.: Lymphosarcoma of the Larynx, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 45:578, 1936.

10. Cutler, M.: Cancer of the Larynx, Jour. Am. Med. Assn. 115:1339, 1940.

11. Figi, F. A., and Thompson, L.: Rhinoscleroma, Jour. Am. Med. Assn. 91:637, 1928.

12. Foster, J. H.: Papillomatosis Laryngis, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 42:548, 1933.

13. Foster, J. H.: Treatment of Laryngeal Papillomatosis, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 46:786, 1937.

14. Gottstein, G.: Scleroma Treated With X-rays, Rhinosklerom. Jahresb. d. Schles. Gesellsch. f. vaterl. cult. 1902, 80:285, Med. Sec., 1903.

15. Harland, W. G. B.: Laryngological Work, Henry Phipps Inst. Rep., 2:87, 1906.

16. Harmer, D., and Finzi, N. S.: Radium Treatment of Intrinsic Carcinoma of the Larynx, Brit. Med. J. 2:886, 1928.

17. Harris, W., and Klemperer, P.: Pathologic Differentiation Between Radiosensitive and Nonradiosensitive Malignant Neoplasms (Treatment by Coutard Method), Arch. Otolaryngol. 28:355, 1938.

18. Imperatori, C. J.: Indications for Different Types of Treatment, Arch. Otolaryngol. 28:585, 1938.

19. Jackson, C.: The Treatment of Cancer of the Larynx, South. Med. Jour. 34:243, 1941.

20. Jungling, O.: Röntgenbehandlung chirurgischer Krankheiten, Leipzig, Hirzel, pp. 235-242, 1924.

21. Koch, J.: Die Bedeut. d. Bestrahlungs technik u. d. Gewebsaufbau f. d. Erfolg d. Röntgen-beh. v. Larynxpap., Arch. f. Ohren-, Nasen- u. Kehlkopfh. 142:83, 1936.

22. Kramer, R.: Treatment of Laryngeal Carcinoma, Laryngoscope, 48:645, 1938.

23. Ledoux and Sluys: Traitément des cancers epitheliaux du larynx, Brussels, Cancer, 5:1, 1928.

24. Lenz, Maurice: Roentgentherapy of Malignant Neoplasms of the Pharynx and Larynx, J. A. M. A. 99:1840, 1932.

25. Lenz, Maurice: Causes of Failure of Roentgen Therapy in Cancer of the Larynx, Am. Jour. Roentgenol. 46:21, 1941.

26. Levitt, W. M.: Deep X-ray Therapy in Malignant Disease, London, Murray, 1930.

27. Martin, H. E.: Surgery of the Nose and Throat, Nelson's Loose Leaf Surgery, 8:504.

28. Martin, H. E.: Selection of Treatment for Cancer of the Larynx, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 49:728, 1940.

29. Myerson, M. C.: Some Phases of Tuberculosis of the Larynx, Trans. Am. Laryngol. Assn. 61:172, 1939.

30. Moore, I.: Further Remarks on Angiomata of the Larynx, Jour. Laryngol. and Otol. 38:57, 1923.

31. New, G. B.: Treatment of Multiple Papillomas of the Larynx in Children, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 30:631, 1921.

32. New, G. B., and Erich, J. B.: Benign Tumors of the Larynx, Arch. Otolaryngol. 28:841, 1938.

33. Quick, D.: Carcinoma of the Larynx, Am. Jour. Roentgenol. 38:821, 1937.

34. Rickmann, L.: Roentgen Behandlung der Larynx Tuberkulose, Leipzig, Thieme, 1924.

35. Schwartz, A. A.: Rhinoscleroma, Arch. Otolaryngol. 21:199, 1935.

36. Simpson, F. E.: Radium in the Treatment of Hemangioma of the Larynx, J. A. M. A. 96:342, 1931.

37. Solomon, I., and Blondeau, A.: Roentgentherapy in Papilloma of the Larynx, Eye, Ear, Nose and Throat Monthly, 14:65, 1935.

38. Tonsey, S.: The Treatment of Tuberculosis of the Larynx and of the Prostate Gland by the X-ray, High Frequency Current and the Cooper-Hewett Light;

Demonstration of Special Apparatus and of a Rapid Method of Skiagraphy, New York Med. Rec. 66:365, 1904.

39. Turner, A. L.: A Case of Lupus of the Larynx Successfully Treated by the External Application of X-rays, Edinburgh Med. Jour. 22:239, 1907.

40. Wright, J., and Strong, L. W.: Some Laboratory Notes on the Presence of Fat and Lipoid in the Lesion of Rhinoscleroma and Particular Variations in Its Pathology, New York Med. Jour. 153:517, 1911.

41. Zange, J.: Strahlenbehandlung der Kehlkopf Tuberkulose, Strahlentherapie 48:705, 1933..

IX

QUININE IN RELATION TO NERVE DEAFNESS*

S. B. Forbes, M.D.

Tampa, Fla.

From Peru three hundred years ago the Countess of Chinchón first broadcast to two worlds the secret of the powdered bark that in other centuries made bitter brew for remote South American Indians and today makes life livable in the tropics. In her honor the great Linnaeus named this strange product cinchona. From Occident to Orient, from Javanese plantations to recently planted Guatemalan acres, from a pound of priceless seed grown deep in an Andean jungle to a Dutch-controlled world monopoly, so moves dramatically across three centuries the unique romance of one of the richest treasures of the tropics.

Quinine, the most frequently used alkaloid of cinchona, takes precedence among the drugs and chemicals capable of causing nerve deafness. That certain substances have a selective action for the auditory apparatus is a phenomenon long familiar to the otologist. As demonstrated by experimental and clinical studies, the auditory nerve is more susceptible to these substances than are the other nerves of special sense.

Idiosyncrasy for drugs is a consideration of prime importance. A small dose of quinine may cause some persons to experience an elevation of temperature, a cutaneous eruption, tinnitus and deafness; others, highly sensitive to the action of the salicylates, may experience a subnormal temperature, dyspnea and impairment of hearing or of vision. Tobacco and alcohol may affect the auditory nerve adversely, as may also oil of chenopodium, morphine, arsenic, mercury, lead, phosphorus, anilin dyes, carbon monoxide and carbon disulfide.[24-28]

Invaluable as the benefactor of the malarial world, quinine is nevertheless a protoplasmic poison[32] that has a particular affinity for the VIIIth nerve. Although most frequently used in the treatment of malaria, it is also employed therapeutically for diseases of the

*Presented as a Candidate's Thesis to the American Laryngological, Rhinological and Otological Society.

upper and the lower portions of the respiratory tract, corneal lesions, Ménière's disease, tic douloureux, influenza, cardiac diseases, various forms of herpes and doubtless many other disease conditions. In addition, it serves as an abortifacient and as an oxytocic.

A wealth of animal experimentation pertaining to the effect of quinine on the auditory apparatus has been reported by numerous investigators. West[31] observed that this drug produces degeneration of the myelin sheath of the auditory nerve when administered in massive doses to rabbits and that in therapeutic doses it causes degeneration in the spiral ganglion and peripheral neuron of this nerve. The experimental work of Covell[2, 3] demonstrated that quinine bisulfate and sodium salicylate produce degenerative changes in the cytologic constituents of the cells of the stria vascularis and the hair cells of the organ of Corti. He noted that while greater alteration of the cells of the spiral ganglia follows the administration of sodium salicylate, the lesions produced by quinine are greater in the cells of the stria vascularis and the hair cells of the organ of Corti. This author also reported significant changes in the values obtained for the relative vascularity in the animals receiving quinine for several weeks; the vascularity of the stria vascularis was increased up to two and one-half times that of the control animals in some groups. Belemer[1] mentioned the altered pressure of the intracochlear fluid owing to the distention of the stria vascularis.

The experiments of Wittmaack,[32] especially with chronic poisoning by prolonged administration, led him to conclude that quinine is a protoplasmic poison having a definite toxic effect on the nerve cells, particularly the cells of the cochlear ganglia and the associated nerve fibers, a condition that may lead to cochlear degeneration and deafness. He also observed that this drug may induce labyrinthine hypotonia as a result of a reflex process in the vegetative nervous system and that its action may have a pronounced effect when in conjunction with concomitant hypertonia. The permanent deafness that occurs in some instances following the administration of the salicylates was ascribed by Haike[14] to the destruction of, or irreparable injury to, the cells of the spiral ganglia. According to Klugkist,[18] deafness owing to alcohol occurs as a result of injury to the hair cells of the organ of Corti with the greatest damage at the basal turn of the cochlea.

The work of Wittmaack[32] and other investigators pertaining to the toxic effect of quinine on the cells of the spiral ganglia of the internal ear is analogous to that of de Schweinitz,[4-7] Holden,[15] Druault[10-11] and others in which they demonstrated experimentally in

dogs the pathologic changes in the cells of the retinal ganglia owing to this drug. De Schweinitz[4-7] observed that the primary effect is on the vasomotor centers, causing constriction of the vessels and finally changes in their walls and that there is also a special selective action on the optic nerve. Holden[15] noted constriction of the retinal vessels and degeneration of the cells of the retinal ganglia and their axis-cylinder processes. He concluded that it is not possible to determine to what extent this degenerative change may arise from the direct toxic action of the cinchonized blood and in what measure it may result from the indirect toxic action of quinine in constricting the retinal vessels and thus reducing their nutritive supply. Rapid and early degeneration of the cells of the retinal ganglia was the outstanding observation of Druault.[10-11] He concluded that blindness owing to quinine results primarily from the toxic effect of the drug on these cells and on the optic nerve with vasoconstriction serving as a contributory process in bringing about the degenerative changes.

Additional experimentation with animals established that quinine, administered by whatever method, may reach the brain and the spinal fluid. Kirstner and Pantchenkoff[17] observed that this poison, when administered orally to rabbits, occurs in higher concentration in the brain than in any other organ and apparently may be taken up both by the brain and by the peripheral nerves. Vogt[30] noted that it enters the brain substance from the blood more easily than it enters the cerebrospinal fluid. In his report of an experimental study Manca[19] stated that although this drug is demonstrable in the cerebrospinal fluid after administration orally, intravenously and intramuscularly, it occurs in the highest concentration following intravenous injection.

As useful as quinine has proved to be therapeutically, its role in relation to deafness might well be carefully investigated in the light of the knowledge gained by experimental work. It appears that this protoplasmic poison may affect the cortical center of hearing, the central nerve paths, the auditory nerve and the internal ear. Indeed, it probably acts on all four. Having a definite toxic action on the cells of the spiral ganglia and seeming to have a special affinity for the external hair cells of the basal turn of the cochlea, this drug not only acts as a protoplasmic poison but also as a vasoconstrictor. From the resulting ischemia there may develop a lack of nutrition owing to the anoxemia, and there may follow an atrophy of degeneration of both the organ of Corti and the spirial ganglia. Ischemia is likewise doubtless the cause of damage to the retina,

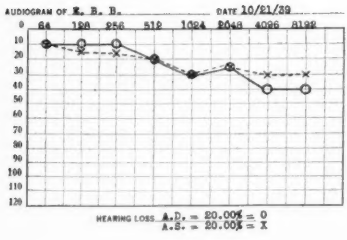


Fig. 1.

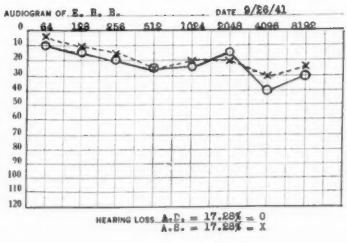


Fig. 2.

Fig. 1.—E. B. B., a boy aged 8, from infancy gave evidence of impaired hearing and amblyopia, which was confirmed by examination when he was 5½ years of age. His mother was given quinine at hourly intervals during the 24 hours immediately preceding delivery at the time of his birth. The audiogram shows the impairment of hearing, especially for the high tones, when the child was 8 years old.

Fig. 2.—A second audiogram, made two years later when E. B. B. was 10 years of age, shows no further loss of hearing.

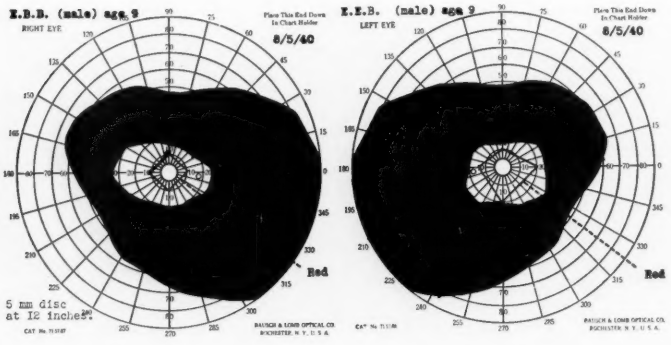


Fig. 3.—The charts show the visual fields of E. B. B., whose audiograms are shown in Figs. 1 and 2. At the time of this examination he was 9 years of age. The vision was 20/30 for each eye whereas three and one-half years previously it was 20/50 for each eye. Pallor and loss of detail were evident in the nerve heads, but no vascular change could be discerned.

especially to the nerve fibers and the ganglion cell layer and perhaps the inner nuclear layer. Some authors concluded that it damages the rods also as the peripheral vision is involved. Wunderlich[33] concluded that quinine injures the nerve elements primarily, the vascular constriction and ischemia being either secondary or concomitant. Elliott[12] reviewed the literature on ocular lesions and visual disturbances caused by poisoning from quinine.

The notable investigation of Mosher,[20] carried out on pregnant animals, demonstrated the damaging effect of quinine on the delicate mechanism of the fetal ear. He noted hemorrhages of the scala vestibuli, the semicircular canals and the scala tympani in the cochlea of the fetus when the mother had been given quinine orally or by injection. He observed further that the mesenchymal tissue surrounding the ossicles, the tissue covering the cochlea, especially at its base, and the mesenchymal tissue lining the bulla cavity are the preferred sites for hemorrhage into the mesenchymal tissue of the ear. Following the experimental administration of quinine and the salicylates to pregnant animals, Covell[2] observed lesions in the hair cells of the organ of Corti of the fetal guinea pig that were similar to those of the adult animal although more extensive.

Recently Taylor, Dyrenforth and Pollard[29] demonstrated the absorption of quinine into the cerebrospinal fluid of the human fetus in utero. Previously Taylor[24-28] had suggested quinine, used in ante partum medication, as a possible etiologic factor of deafness in the newborn and had supplied ample clinical evidence indicating that this drug, when administered to the mother during pregnancy, whether in the treatment of concurrent disease, as an abortifacient or as an oxytocic, may cause deafness in the child, either partial or complete. He reported several cases of deafness in children that he believed to be of this origin. Richardson[23] later reported two cases, one of amblyopia and one of amaurosis, in children whose mothers had been treated with quinine during pregnancy, in the one instance for malaria and in the other for the purpose of inducing labor. As early as 1909 Nicloux[21] established that the human placenta acts as a dialyzer, thus permitting crystalloid substances such as quinine to pass through the epithelium of the placental villi into the fetal circulation. Dilling and Gemmell[8, 9] reported finding quinine in the urine of babies whose mothers had been given this drug to induce labor. Regnier[22] found the concentration of this poison comparatively high in the blood and higher in the brain than in the liver of a fetus of four and a half months after the mother had been given 1.5 gm. of quinine sulfate forty hours previously. In a case of fetal

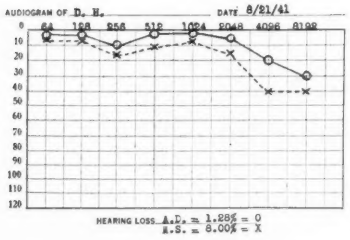


Fig. 4.—D. H., aged 7, the daughter of the medical missionary and his wife whose audiograms are described, had been given quinine from infancy as a prophylactic against malaria. Also, her mother had taken the drug regularly for the same purpose throughout the term of pregnancy with each of her three children. The audiogram of this child shows definite nerve deafness characterized by loss of hearing for the high tones. Audiograms of the brother and sister, reared under the same conditions, gave no evidence of impaired hearing.

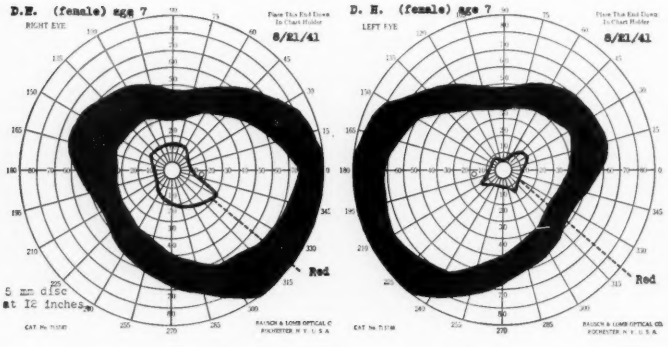


Fig. 5.—The charts of the visual fields of D. H., whose audiogram is shown in Fig. 4, illustrate the contraction for form and color. The vision was 20/50 for each eye. The eyegrounds showed fine vessels only.

death from quinine given the mother, King[16] discovered the drug in the brain and in the urine of the fetus in considerable quantity. Thus it seems reasonable to conclude that ante partum therapy with this protoplasmic poison may damage the ear of the unborn child permanently because of the pathologic changes it is capable of producing. Four illustrative cases are included in my series.

The estimate of the number of persons in the United States suffering from deafness varies from 10,000,000 to 20,000,000. It is generally conceded that at least 3,000,000 children are handicapped by impaired hearing. According to a statement of the Public Health Service,[34] some degree of deafness in one or both ears is experienced by approximately one third of all adults, and some impairment of hearing is suffered by 15 per cent of the school children, nearly half of this number having a serious loss of hearing. Thus one child in every six or seven strains to hear what goes on in the classroom and is hindered by a hearing defect of one kind or another. How nearly the estimates approach the actual number of deaf persons in this country is open to question, but there is reason to believe that they may be too low, particularly with reference to children and deaf mutes.

The results of the enumeration of the blind and of deaf mutes, made in connection with the Fifteenth Census, 1930, are presented in a bulletin of the Bureau of the Census entitled "The Blind and Deaf-Mutes in the United States, 1930." From the introduction the following paragraph is taken:

> "No high degree of accuracy is to be expected in a census of the blind and of deaf-mutes carried out by the methods which it has been necessary to use thus far in the United States. The reasons for this are that even with careful definitions of the groups to be included a large element of personal judgment enters into the decision of an enumerator as to whether a given individual should be reported as blind or as a deaf-mute; and inconsistencies follow from the varying degrees of intelligence and persistence of enumerators. Added to this, there is a tendency on the part of relatives to conceal the presence of blind persons or deaf-mutes in their families, especially in the case of children. Because of these conditions, and of changes made from time to time in definitions, as well as in the administrative methods used in taking the census, the enumeration of the blind and of deaf-mutes has doubtless always been more or less inaccurate and incomplete. That must be borne in mind in dealing with the figures presented herein, particularly in comparison with those of the 1920 enumeration."[35]

It has been suggested that if the same proportion exists between the deaf population and the number of children in schools for the deaf as between the general population and the number of children in all schools (27,947,009 : 137,008,435 :: 18,767 : x), the num-

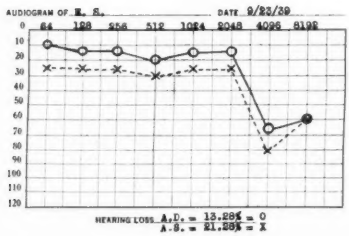


Fig. 6.—E. S., aged 21 when examined, had been given massive doses of quinine when 8½ years of age and had thereafter experienced a loss of hearing and of vision to a considerable degree. The audiogram shows the extent of the impairment of hearing, which is largely nerve deafness with characteristic loss of perception for the high tones.

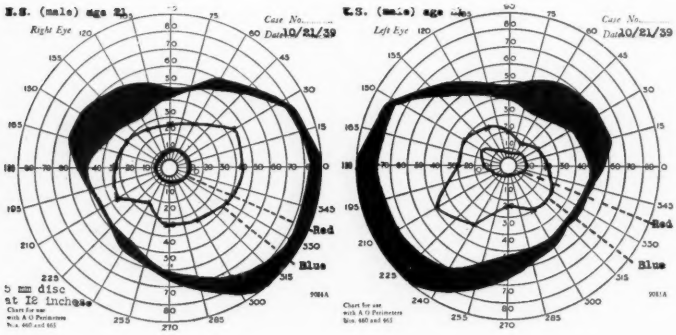


Fig. 7.—The charts show the visual fields of E. S., whose audiogram is shown in Fig. 6. Examination of the eyegrounds revealed the characteristic changes that may occur following quinine therapy. The vision was 20/100 for each eye and was not improved by glasses.

ber of deaf mutes recorded in the census of 1930 should be 92,004 instead of 57,084.[36] Enumerators for the census of 1930 were required to "include as a deaf mute (1) any child under 8 years of age who is totally deaf, and (2) any older person who has been totally deaf from childhood or was born deaf."

From a summarized report[36] of the Committee on Hard of Hearing of the American Society for the Hard of Hearing for the years 1936-1937 and 1937-1938, based on incomplete information from sources not scientifically controlled, one gleans that in the year 1936-1937 the percentage of school children with impaired hearing in the malarious states was approximately 5.5 per cent and in the so-called nonmalarious states 5.8 per cent. For the following school year the figures were more than reversed as the percentage for the malarious states was approximately 6.7 per cent and for the nonmalarious states 5.5 per cent.

Statistics, then, are largely meaningless unless gathered under a plan of rigorous scientific control. No otologist can doubt, however, the widespread prevalence of deafness nor be unmindful of the grave economic and social problem that follows in its wake. If any prophylactic measures can be taken to alleviate this distressing situation, they should be made known at once and should be put to immediate use. The mother whose child is totally or partially deaf, the adult who is handicapped by partial or complete loss of hearing, the otologist who is called upon to treat these patients, all care little for statistics in the aggregate from uncertain sources, but they are deeply concerned with causes and alleviation and prevention.

From among the cases coming under my observation over a period of seventeen years 1,563 cases of all types of deafness as they come in routine office practice, including 356 cases of nerve deafness, were selected for study. In each case the history was carefully scrutinized, a questionnaire was sent to the patient in cases in which additional data were desirable, and in many instances the patient was interviewed personally in the interest of the survey. No effort was spared to make the study as scientifically correct as possible.

It transpired that the records of 316 cases of nerve deafness, carefully differentiated from mixed types of deafness, and 1,085 cases of all other types of deafness could be satisfactorily analyzed. In 109 of the 316 cases of nerve deafness, or 34.5 per cent, there was a history of the ingestion of quinine over a considerable period of time. In 22, or 6.9 per cent, the patients gave as their personal opinion that quinine had caused the deafness, and in 7, or 2.2 per

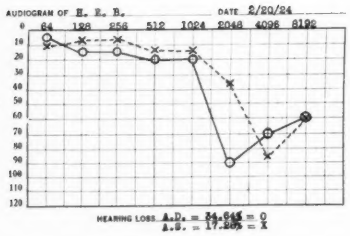


Fig. 8.

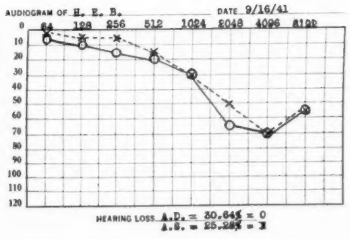


Fig. 9.

Fig. 8.—H. E. B., aged 73 when last examined, had had repeated attacks of malaria, including black water fever, while serving as a missionary in Africa over a period of many years. Following frequent ingestion of large doses of quinine during that time he always experienced tinnitus and deafness. This audiogram was made upon his return from Africa in 1924, when he was 56 years of age, and illustrates the characteristic loss of perception for the high tones. An audiogram recently made is shown in Fig. 9.

Fig. 9.—The second audiogram of H. E. B. was made in 1941, when he was 73 years of age. In the interim of seventeen years he had taken no quinine. Despite his age, there was no evidence of real progression in the deafness.

cent, the patients related that a single course of quinine therapy, in which the drug had been ingested in large doses, had resulted in sudden and permanent impairment of hearing. In but 93, or 8.5 per cent, of the 1,085 cases of all types of deafness other than nerve deafness had the patients taken quinine, and in only 2, or .18 per cent, of these cases was the drug associated with the deafness in the mind of the patient.

It is striking and certainly not without significance that in a series of 1,401 cases of deafness of all types quinine was a factor to be considered in 34.5 per cent of the 316 cases of nerve deafness and in but 8.5 per cent of the 1,085 cases of other types of deafness, the percentage in the former being approximately four times as great. Especially are these percentages significant in that the cases of deafness other than nerve deafness exceeded those of nerve deafness by almost three and one-half times.

Analysis of this series showed, as the accompanying illustrations demonstrate, that quinine early causes a loss of perception for the high tones. Thus evidence is offered of its effect on the first turn

of the cochlea. As these tones are above the conversational range, the average person does not recognize the loss. It is only when the impairment progresses far enough for the loss to be perceptible within the range of the voice that the deafened person becomes aware of the defect and turns to the otologist as a rule. The damage is then irreparable because of the degenerative changes described.

Four cases of so-called congenital deafness, previously reported, have come under my observation in children whose ages ranged from 20 months to 5½ years. In two of these cases, during pregnancy the mothers had taken quinine continuously for a considerable period of time in the treatment of malaria. In the third case the mother had taken quinine as an abortifacient. The child, brought to me for examination when he was 37 months old, was suffering from amblyopia and impaired hearing. The parents stated that he had always held objects very close to his eyes, was accustomed to bump into things and had never seemed to hear well. There was a pronounced fixation nystagmus, the vision was greatly limited, and examination of the eyegrounds revealed intense pallor of the disks with loss of detail and small retinal vessels. There was definite impairment of hearing, but to what degree was difficult to determine.

In the fourth case the attending physician had repeatedly given the mother quinine at hourly intervals during the 24 hours immediately preceding delivery in order to induce labor. When I first examined the child, a boy aged 5½, the mother related that at an early age he had begun to hold objects close to his eyes and to look sideways or out of the top of the eyes. Too, she had soon noticed that his hearing was defective. Examination confirmed the presence of amblyopia and impaired hearing. There was a very noticeable fixation nystagmus; the vision was 20/50 for the right eye and 20/50 minus for the left eye. There was pallor of the nerve heads, but no vascular change, and a low grade hyperopic astigmatic error was present. Aural examination gave negative results. Audiograms made at that time, though not satisfactory, showed a loss of hearing, particularly for the high tones. After two and one-half years the patient was again examined. An audiogram made at this time is shown in Fig. 1; a second audiogram made two years later, when the boy was 10 years old, is shown in Fig. 2. Charts of the visual fields, made when he was 9 years of age, are shown in Fig. 3.

It was my privilege recently to examine a medical missionary, his wife and three children, who returned in June, 1941, from Lusambo, Belgian Congo, where he has had charge of a mission hos-

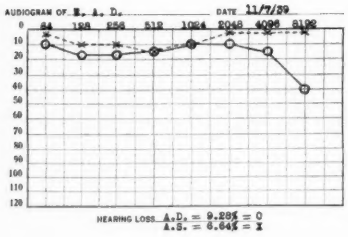


Fig. 10.

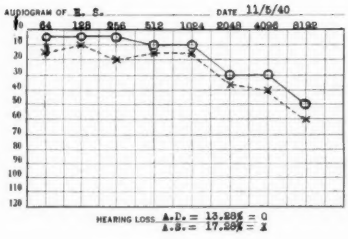


Fig. 11.

Fig. 10.—E. A. D., aged 63, had experienced tinnitus in the right ear for several months prior to examination. He had taken quinidine for a long time in the treatment of a mild cardiac condition. There was nothing else in the history of possible etiologic significance, and examination gave negative results. This audiogram made in 1939, shows a loss of hearing in the right ear for the highest tone. An audiogram made two years later gave no evidence of progression of the deafness. In the interim no quinidine had been taken.

Fig. 11.—R. S., aged 52, complained of tinnitus and loss of hearing in both ears. She had taken quinidine for several months in the treatment of cardiac disease. The hearing was not improved after the drug was discontinued. The audiogram shows the degree of impairment.

pital for twelve years. The son, aged 10, and the daughters, aged 9 and 7, were born there. The entire family has taken quinine routinely through the years as a prophylactic against malaria, the mother taking it throughout the three terms of pregnancy and the children taking it from infancy in doses proportionate to age. The father, aged 38, regarded his hearing as particularly acute and was greatly surprised to observe from the audiogram evidence of an early nerve deafness, for the loss of perception was characteristically for the high tones. A change of lesser degree, likewise showing decreased perception for the high tones, was demonstrated in the audiogram of the mother. Examination of the ears and eyes of the two older children gave normal results. In the audiogram of the youngest child definite nerve deafness with defective perception for the high tones was revealed (Fig. 4). Also, distinct contraction for form and color was evidenced in the chart of the visual fields (Fig. 5); the vision was 20/50 for each eye with no appreciable error of refraction. The eyegrounds showed little except extremely fine vessels. No member of the family had a history of disease of

the ear, eye, nose or throat, and the examinations were confirmatory. The results of these examinations are highly suggestive of idiosyncrasy for quinine.

An audiogram and a chart of the visual fields of a young man, aged 21 when examined, whose hearing and vision had failed greatly following the ingestion of massive doses of quinine at the age of 8½ years, are shown in Figs. 6 and 7. Particularly interesting are two audiograms (Figs. 8 and 9), made 17 years apart, of a missionary to Africa who repeatedly took large doses of quinine in the treatment of malaria and black water fever. Despite the patient's age of 73 years when the second audiogram was recently made, there had been no real progression in the deafness since quinine therapy was discontinued upon his return from Africa in 1924.

One patient, a man aged 48, had, during the first of the two years he had experienced deafness and tinnitus, taken bromoquinine with great frequency for nervousness, insomnia, chills and fever.

The otologist must now take cognizance of quinidine, another frequently used alkaloid of cinchona, as a possible cause of aural symptoms.[13] Described as slightly more toxic, perhaps, than quinine and fully as potent as an antimalarial, although used comparatively rarely for this purpose, this drug is tolerated in numerous instances by patients who have an idiosyncrasy for quinine. Its most important and extensive use is in the management of auricular fibrillation and certain other forms of irregularity of the heart, but treatment often has to be discontinued because of unpleasant symptoms such as increased palpitation, precordial pain, headache, nausea or vomiting, and tinnitus. The audiogram shown in Fig. 10 illustrates the suggestive etiologic role of quinidine. The patient had been taking quinidine for many months in the treatment of a mild cardiac ailment and complained of tinnitus of several months' duration. Examination revealed a loss of perception for the highest tone. The drug was discontinued. A second audiogram, made two years later, showed no progression of the deafness. Another patient, whose audiogram is shown in Fig. 11, took quinidine over a period of several months in the treatment of a cardiac condition. A considerable degree of tinnitus developed in both ears, and there was definite loss of hearing, which has not improved since the discontinuance of the drug.

How much quinine may be safely taken? Doubtless in more instances than is generally believed the drug is definitely contraindicated; in some instances it may be that very small doses may

safely be administered, and in other instances it may be that no harm follows its use in moderation. Certainly it is generally to be avoided in massive doses. Idiosyncrasy for the drug appears to be the determining factor.

Certainly the drug is to be reckoned with in otology as it has not been in the past. Its use appears not to be abating for the normal consumption in this country holds at approximately 4,700,000 ounces a year.[13, 37] Despite wide fluctuation in the consumption of quinine owing to variation in the prevalance of malaria, there is reason to believe that more of it was used in the southern states during the last decade than in the preceding one.[13] In addition to its usual therapeutic uses, it is an ingredient of wine tonics, hair tonics and proprietary remedies, both well known and obscure, that continue to be marketed successfully, particularly in the deep South. In view of the fact that this valuable drug has an established place in the physician's armamentarium and in the mind of the laity, the otologist must be on guard for he can ill afford to be unmindful of the implications of its use in relation to deafness.

SUMMARY

It is well established that quinine has a predilection for the auditory nerve and is capable of causing nerve deafness. Its damaging effect on the delicate mechanism of the fetal ear has also been demonstrated experimentally.

Idiosyncrasy for this drug is an important consideration not sufficiently stressed in the etiology of nerve deafness.

The perception for the high tones is first affected, and the patient is often unaware of the impairment of hearing because these tones are beyond the conversational range.

In a series of 1,401 cases of all types of deafness, selected because they could be satisfactorly analyzed, 316 were cases of nerve deafness and 1,085 were cases of all other types of deafness. In 109 of the 316 cases of nerve deafness there was a history of the ingestion of quinine over a considerable period of time; in 22 of the 109 cases the patients regarded quinine as the cause of the deafness; in 7, they ascribed the sudden and permanent impairment of hearing they had experienced to a single course of therapy with this drug taken in large doses. In only 93 of the 1,085 cases of all other types of deafness was there a history of the ingestion of quinine, and in but 2 cases was the deafness even associated with this

drug by the patient. Thus in 34.5 per cent of the cases of nerve deafness quinine was a significant factor while in only 8.5 per cent of the much larger group of cases of all other types of deafness was it to be considered.

It appears that in some instances quinine may cause permanent impairment both of hearing and of vision when administered in large doses.

Experimental evidence and clinical observations support the view that quinine administered to the mother during pregnancy may cause deafness and amblyopia in the child.

Audiograms and charts of visual fields which are presented suggest the role of quinine as an etiologic factor of nerve deafness and as a causative agent of amblyopia as well.

It is suggested that quinidine may be a cause of nerve deafness. Two audiograms are shown in support of this view.

409 Citizens' Building

REFERENCES

1. Belemer, J. J.: Vessels of the Stria Vascularis with Special Reference to Their Function, Arch. Otolaryng. 23:93-97 (Jan.) 1936.

2. Covell, W. P.: A Cytologic Study of the Effects of Drugs on the Cochlea, Arch. Otolaryng. 23:633-641 (June) 1936.

3. Covell, W. P.: Effects of Drugs on the Stria Vascularis, Arch. Otolaryng. 27:438-443 (April) 1938.

4. de Schweinitz, G. E.: Concerning Quinine Blindness, With the Report of a Case, Arch. Ophth. 39:101-106, 1910.

5. de Schweinitz, G. E.: Toxic Amblyopias: Their Classification, History, Symptoms, Pathology and Treatment, Philadelphia, Lee Brothers, 1896.

6. de Schweinitz, G. E.: Additional Experiments to Determine the Lesion in Quinine Blindness, Trans. Am. Ophth. Soc. 23:29, 1891-1893.

7. de Schweinitz, G. E.: Some Experiments to Determine the Lesions in Quinine Blindness, Trans. Coll. Phys., Ser. 3, 12:185-193, 1890.

8. Dilling, W. J., and Gemmell, A. A.: A Preliminary Investigation of Foetal Deaths Following Quinine Induction, J. Obst. & Gynaec., Brit. Emp., 36:353, 1929.

9. Dilling, W. J., and Gemmell, A. A.: Further Investigations of the Death of the Child Following Induction of Quinine, J. Obst. & Gynaec. Brit. Emp., 37:528, 1930.

10. Druault, A.: Recherches sur la pathogenie de l'amaurose quinique, Thesis, Paris, 1900.

11. Druault, A.: Recherches sur l'amaurose quinique, Arch. d'opht. 22:19-32, 1902.

12. Elliot, R. H.: Quinine Poisoning: Its Ocular Lesions and Visual Disturbances, Am. J. Ophth. 1:547-650, 1918.

13. Forbes, S. B.: The Etiology of Nerve Deafness with Particular Reference to Quinine, South. M. J. 33:613-621 (June) 1940.

14. Haike, H.: Experimentelle Untersuchungen zur Kenntnis der Wirkung des Natrium salicylicum auf das Gehoerorgan, Arch. f. Ohrenh. 63:72, 1904.

15. Holden, W. A.: The Pathology of Experimental Quinine Blindness, Trans. Am. Ophth. Soc. 8:405-411, 1897-1898; Arch. Ophth. 27:583-592, 1898.

16. King, E. L.: Does Quinine in the Induction of Labor Have a Deleterious Effect on the Fetus?, J. A. M. A. 101:1145 (Oct. 1) 1933.

17. Kirstner, A. A., and Pantchenkoff, M. M.: Distribution of Quinine in the Organism, Klin. med. 9:751-758, 1931.

18. Klugkist, H.: Ueber die Alkohol-Vergiftung des Gehoerorgans, Thesis, Goettingen University, 1928.

19. Manca, S.: Permeability of the Central Nervous Barrier to Quinine: Experimental Study, Riv. di malariol, (Sezione I) 13:601-608, 1934.

20. Mosher, H. P.: Does Animal Experimentation Show Similar Changes in the Ear of the Mother and the Fetus after Ingestion of Quinine by the Mother? Laryngoscope 48:361-395 (June) 1938.

21. Nicloux, M.: Le passage des substances chimiques de la mere au foetus, Obstetrique 2:840, 1909.

22. Regnier, M. T.: De la permeabilite placentaire aux substances medicamenteuses et toxiques: quinine, Compt. rend. Soc. de biol. 120:1089-1090, 1935.

23. Richardson, Shaler: The Toxic Effect of Quinine on the Eye, South, M. J. 29:1156-1164 (Dec.) 1936.

24. Taylor, H. M.: Nerve Deafness of Known Pathology or Etiology: Deafness from Drugs and Chemical Poisons, Laryngoscope 47:692-705 (Sept.) 1937.

25. Taylor, H. M.: Prenatal Medication and Its Relation to the Fetal Ear, Surg., Gynec. & Obst. 64:542-545 (Feb.) 1937.

26. Taylor, H. M.: Further Observations on Prenatal Medication as a Possible Etiologic Factor of Deafness in the New Born, South. M. J. 28:125-130 (Feb.) 1935.

27. Taylor, H. M.: Prenatal Medication as a Possible Etiologic Factor of Deafness in the New Born, Arch. Otolaryng. 20:790-799 (Dec.) 1934.

28. Taylor, H. M.: Does Quinine as Used in the Induction of Labor Injure the Ear of the Fetus?, J. Florida M. Assn. 20:20-23 (July) 1933.

29. Taylor, H. M., Dyrenforth, L. Y., and Pollard, C. B.: Absorption of Quinine into the Cerebrospinal Fluid of the Fetus in Utero, J. Florida M. Assn. 27:487-491 (April) 1941.

30. Vogt, M.: Distribution of Medicaments in Various Regions of the Central Nervous System and Their Microdetermination in Tissue, Arch. f. exper. Path. u. Pharmakol. 178:560-576, 1935.

31. West, R. A.: Effect of Quinine upon the Auditory Nerve, Am. J. Obst. & Gynec. 36:241-248 (Aug.) 1938.

32. Wittmaack, K.: Ueber Chinin Wirkung in Gehoerorgan, Ztschr. f. Hals-, Nasen- u. Ohrenh. 39:211-222 (Jan.) 1936.

33. Wunderlich, G.: Die Chininintoxikation und ihre Pathogenese, Klin. Monatsbl. f. Augenh. 64:270-286, 1920.

34. Public Health Bull. 7139, U. S. Treasury Department, Public Health Service.

35. The Blind and Deaf-Mutes in the United States, 1930, Bull. of the U. S. Department of Commerce, Bureau of the Census, Washington, 1930, Introduction.

36. Report of the Committee on Hard of Hearing Children of the American Society for the Hard of Hearing for the School Year 1937-1938, American Society for the Hard of Hearing, Pamphlet No. 122.

37. World Trade Notes on Chemical and Allied Products, U. S. Department of Commerce, Bureau of Foreign and Domestic Commerce, Chemical Division, 13:318 (May 13) 1939.

X

SULFANILAMIDE IMPLANTATION IN MASTOID WOUNDS*

RAYMOND H. MARCOTTE, M.D.

NASHUA, N. H.

It is generally accepted that sulfonamide therapy has reduced the incidence of mastoiditis. Numerous articles published during the last three years attest to this fact. Observations by Bowers,[1] Harkness,[2] Lindsay,[3] Galloway,[4] Maybaum,[5] Boies,[6] and numerous others have definitely proved that given an acute otitis media, if a myringotomy is indicated and promptly performed and a sulfonamide compound is given internally, the sulfonamide will exert a beneficial effect on the healing of the infected ear, shorten the course of illness, and reduce the possibility of mastoiditis and other complications.

Unfortunately, the otologist does not always see the otitis media in its early stage, and frequently mastoiditis has complicated the illness when he is consulted. The sulfonamide compounds do not concentrate in osseous tissue. The patients who have not received early treatment with a sulfonamide drug and whose mastoid cells are already invaded by the infection will not do any better with these drugs, so far as the mastoid is concerned, and essentially the same proportion will come to surgery as did before the advent of the new compound. We have all seen early stages of mastoiditis respond favorably to conservative treatment: absolute rest, improved middle ear drainage, even in the presence of positive roentgen findings and mastoid tenderness. But, in this group, we have been properly warned of the danger in the indiscriminate use of sulfonamide therapy, as it may obscure the diagnosis and result in masked or latent involvement of the mastoid and adjacent structures.

The results reported far and wide by general surgeons in acute abdominal and pelvic surgery, then by military surgeons in traumatic war wounds of the head, trunk or extremities, of direct implantation of the sulfonamide compounds seem to warrant its trial in mastoid surgery. Hoyt,[7] Key,[8] and Toumey[9] report most encour-

---

*Presented before the Eastern Section Meeting of the American Laryngological, Rhinological and Otological Society, Hartford, Conn., January 15, 1943.

aging results in osteomyelitis following adequate surgery plus local implantation of sulfanilamide in the wound. The drug exerts a local bacteriostatic effect and may stimulate local tissue resistance.

Livingston[10] has reported a series of 13 patients operated upon for acute mastoiditis followed by the implantation of sulfonamide derivatives and tight closure. His results show that 11 wounds healed by primary union within 6 days, and 2 drained for a period of 30 days. Bryant[11] reports similar results on a group of 15 patients, including several with chronic otitis media preceding the mastoidectomy. Maxwell[12] reported a series of 10 simple mastoidectomy wounds treated by the local application of sulfanilamide powder at the time of operation and partial closure. His results also were highly satisfactory. Guerry and Putney[13] report 20 similarly treated cases with a control group of 20 mastoidectomies without sulfanilamide implantation. The groups treated with sulfanilamide had a drainage period of 52.8 per cent less than that in the control series, while postoperative hospitalization was reduced on an average of 55 per cent.

None of these patients showed any systemic reaction from absorption of the drug, and repeated blood concentration tests have demonstrated very small amounts present in the blood stream. Livingston[10] reported two patients with a maximum blood concentration of less than 5 mg. per 100 cc. 24 hours after local implantation, reduced to less than 1 mg. per 100 cc. in 72 hours. Guerry[13] reported that in most patients none of the drug was found in the blood, while in a few a trace was found, the highest determination being 0.7 mg. per 100 cc. None was found in two of my patients who did not receive sulfonamides by mouth.

The observations that I am reporting today were made on a series of 12 mastoidectomies performed during the past 18 months. The patients consisted of 11 children, the youngest three months, the oldest twelve years of age, and one adult, aged 52. They either consulted me or were referred to me because of prolonged ear drainage or postauricular swelling. Seven had postauricular swelling; one had Bezold's mastoiditis; all had definite roentgen and clinical findings of mastoiditis.

The bacteriological reports on cultures and smears taken directly from the mastoid wounds were: eight streptococci and two pneumococci growths; two specimens were received dry and showed no growth after 72 hours. One patient, aged eight, had a definite thrombosis with a large perisinuous abscess and marked necrosis of

the sinus wall; the sinus plate was removed extensively without exposing normal, bluish sinus wall. His white cell count was 28,000 on admission to the hospital, and 36,000 following a chill 24 hours after operation. This was reduced to 15,000 on the fourth day and 9,000 on the sixth day. His temperature was normal from the third day on.

All these patients were treated alike. A simple mastoidectomy was performed with exenteration of the mastoid cells, and drying of the wound was followed by the implantation of sulfanilamide powder in the cavity. Sulfanilamide powder was the drug of choice, as sulfathiazole may cake in the presence of a purulent discharge and act as a foreign body. The wound was then closed, except for a small piece of rubber dam inserted down to the antrum, which was removed in 48 hours and replaced by another, also removed in 48 hours. Alternate sutures were removed on the fourth day and the remaining ones on the seventh day.

Four steps are noted here: (1) proper exenteration of the mastoid wound, (2) drying of the bleeding points, (3) insufflation of the sulfanilamide powder, (4) partial closure with a rubber drain.

No general toxic manifestations were noted from the local use of the sulfonamide in any of these patients. The wound in every instance healed by first intention. The dressings were never wet and only slightly discolored, except at the first dressing. These dressings were done every 48 hours, at which time a small amount of sulfanilamide powder was introduced into the wound by means of a powder blower through the rubber drain opening. By the tenth day every wound was closed and dry and so was the middle ear. The frequent stitch abscesses encountered in mastoid surgery, with a resulting breaking down of the wound and prolonged, profuse drainage, were invariably absent and the morbidity was reduced more than 50 per cent.

All but two of these patients received a sulfonamide compound internally immediately after operation, and no doubt the favorable progress of the disease was influenced in part by this. However, a series of mastoidectomies performed by me during the previous three years under the same conditions, except for the local implantations, presented the same dressing problems as heretofore, although mastoid complications had been reduced.

The adult patient, whose case history follows, demonstrated another good indication for local chemotherapy following mastoidec-

tomy, namely: an idiosyncrasy for the drug, contraindicating its internal administration.

CASE 1.—An adult male, aged 52, presented himself on July 23, 1942. This patient has been subject to recurrent ear abscesses since childhood. He had been treated last winter for an abscess of right ear, at which time sulfadiazine gr. 30 was given. One dose caused a violent reaction: convulsions, nausea and vomiting, apparently due to idiosyncrasy. Subsequently the patient gave a history of idiosyncrasy for numerous drugs, such as aspirin and morphine. The sulfadiazine was discontinued and the ear abscess healed without any complications.

Two months ago the patient had another abscess of the same ear and was treated by the family physician at home. Drainage of the ear persisted and furunculosis of the canal developed. This was treated locally by his physician. When I saw the patient two days before the operation, what appeared to be a large furuncle just below the pinna was incised and drained. The draining continued and the canal around the drum became narrowed and the ear drum itself remained thickened with a small amount of serosanguineous discharge from middle ear. A severe right temporal headache developed. The patient was sent to the hospital for an x-ray film which showed marked sclerosis and cavitation of the right mastoid. The blood count was 18,000.

A mastoidectomy was performed under general anesthesia. The usual incision was made and exploration of the cortex showed it to be intact. The cortex was very thick and hard, indicating past mastoid involvement. Near the roof of the mastoid, almost half an inch below the cortex, a large abscessed cavity filled with thick purulent discharge was exposed. The roof of this abscess was formed by necrosed dural plate, which was removed, exposing an area two centimeters in diameter of dura covered with granulations. Adequate drainage from the middle ear through the antrum was established. The roof of the tip was removed and a large cavity posterior to the tip was cleaned of granulation tissue and purulent material. Sulfanilamide powder was implanted and a rubber drain was inserted down to the antrum and the wound was partially closed with silkworm. The abscess near the pinna, which appeared to be a subcutaneous affair, was reincised, cleaned and proved to be much deeper than suspected. Although the floor was not reached, it probably extended to the region between the tip of mastoid and the parotid gland. This cavity was cleaned out and insufflated with sulfanilamide. The postoperative progress was uneventful. The wound healed by first intention and the middle ear was dry on the fourth day. The temperature remained normal throughout convalescence. The sutures were removed on the fourth and seventh days and the patient was discharged on the tenth day.

SUMMARY

1. A properly-managed acute otitis media will probably not develop into mastoiditis.

2. When a mastoidectomy is necessary, sulfanilamide implantation directly into the wound will considerably shorten the morbidity.

3. It is reasonable to expect a better functioning ear if the drainage period from the middle ear and mastoid wound is reduced 50 per cent.

4. These conclusions must be guardedly arrived at until a sufficient number of cases are available over a number of years, as the virulency of the organisms invading the ears varies with the seasons and the years.

196 Main Street

REFERENCES

1. Bowers, W. C.: Observations on 793 Cases of Acute Purulent Otitis Media, J. A. M. A. 115:178-181 (July 20) 1940.

2. Harkness, G. F.: Complications of Surgical Treatment of Acute Mastoiditis, Arch. Otolaryng. 32:915-924 (Nov.) 1940.

3. Lindsay, J. W.: Sulfanilamide Therapy with Special Reference to Ear Infections, Med. Ann. Dist. Col., 9:115-119 (Apr.) 1940.

4. Galloway, T. C.: Chemotherapy, Arch. Otolaryng. 30:901-913 (Dec.) 1939.

5. Maybaum, J. L., Snyder, E. R., and Coleman, L. L.: Experiences with Sulfanilamide Therapy for Otogenous Infections, Arch. Otolaryng. 30:557-575 (Oct.) 1939.

6. Boies, L. R.: Acute Mastoiditis: 1931-1941, Annals of Otology, Rhinology and Laryngology 51:601-610 (Sept.) 1942.

7. Hoyt, W. A., Davis, A. E., and Van Burne, G.: Acute Hematogenous Staphylococcic Osteomyelitis, J. A. M. A. 117:2043-2049 (Dec. 13) 1941.

8. Key, J. A., Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, J. Bone and Joint Surg. 22:952-958 (Oct.) 1940.

9. Toumey, J. W.: Chemotherapy in Osteomyelitis, The Lahey Clinic Bull. 3:12-16 (July) 1942.

10. Livingston, G. S.: Local Sulfonamide Therapy in Acute Mastoiditis, J. A. M. A. 117:1081-1085 (Sept. 27) 1941.

11. Bryant, F. L.: Local Use of Sulfanilamide in Otogenic Infections, Arch. Otolaryng. 35:281-285 (Feb.) 1942.

12. Maxwell, J. H.: The Sulfonamide Drugs in the Treatment of Acute Suppurations in the Middle Ear and Mastoid, Surg. Gyn. and Obst. 74:573-577 (Feb. 16) 1942.

13. Guerry, D. and Putney, F. J.: Local Use of Sulfathiazole in Management of Simple Mastoidectomy Wounds, Arch. Otolaryng. 35:399-407 (Mar.) 1942.

XI

A HEARING AID CLINIC*

B. H. SENTURIA, M.D.
S. R. SILVERMAN, PH.D.
AND
C. E. HARRISON, B.S.

ST. LOUIS

With the increased use of hearing aids as prosthetic agents for those with impaired hearing, a marked need for an impartial evaluation of the comparative efficiency of such devices has arisen. Although recent advances in acoustic engineering have resulted in great improvement in the performance of hearing aids, the prospective user and the otologist are still confronted with the problem of selecting the most satisfactory instrument in any particular case from the many which are available.

In an attempt to shed light on the problem of evaluating hearing aids objectively and impartially in terms of the individual who is to use them, the idea of a hearing aid clinic was conceived by Dr. Max A. Goldstein. Accordingly, such a clinic was established at Central Institute for the Deaf and put into operation in September, 1941. It is the purpose of this paper to describe the operation of this clinic and to report preliminary findings regarding the performance of individual hearing aids in relation to specific categories of defective hearing.

During the past decade, numerous investigators have concerned themselves with the appraisal of hearing aids. Since responses to hearing aids vary according to the type of deafness, it was found necessary to establish appropriate classifications of deafness.

Halsted and Grossman[1] described four types of deafness: (1) middle ear conductive impairment, (2) inner ear conductive impairment, (3) abrupt high tone deafness and (4) deafness due to insufficiency of the acoustic nerve. Holmgren[2] simplified the classification into (1) conductive lesion, (2) cochlear deafness and (3) combined

*From the Central Institute for the Deaf and the Department of Otolaryngology, Washington University Medical School, St. Louis, Missouri.

deafness. A modification of the latter classification used in this report employs the criteria for differential diagnosis outlined by Senturia and Thea.[3]

One of the major obstacles in the adequate evaluation of hearing aids has been the lack of satisfactory testing equipment. In most reports the simple expedient of coupling the transmitter of the hearing aid to the ear piece of the audiometer has been utilized for appraising actual performance. This evaluative technique is scientifically incorrect, since it results in an acoustical mismatch and, in addition, fails to simulate the normal pattern of auditory communication.

Berry[4] reviewed various methods available for testing aids and favored the test whereby the examiner reads and the patient changes his position and adjusts his aid until the distance is determined at which optimum hearing is obtained. Simple voice, word and sentence tests have also been used; however, control of intensity of the sound stimulus presents a troublesome variable in this technique. The Ewings[5] employed speech with the lips of the speaker thirty-six inches from the listener's better ear and with the aid at the same distance from the source of sound. The relative efficiency of these aids was considered first for vowels and then for consonants at various distances and intensities. Sabine,[6] Knudsen[7] and others have also used standard intelligibility tests.

Holmgren,[2] in his clinical approach to the problem, began with a complete otologic examination which included audiometric and loud speaker tests administered at a known and optimum noise level. From this information the selection of a hearing aid was made. The aid was then evaluated by means of intelligibility tests composed of nonsense syllables. In addition, the Kerridge[8] clinic provided for complete air and bone conduction tests in a specially constructed "sound-proof" room. At the conclusion of these tests a letter of instruction directed to the hearing aid agency was given the patient, and a seven-day trial of the recommended instrument was requested. No further follow-up evaluation was reported. Halsted and Grossman[1] supplemented the above technique by testing for above threshold intensities and sound distortion. Number, syllable and sentence tests for intelligibility with and without the aid were also administered.

Disagreement arose with regard to the extent to which the patient's opinion should be used as a criterion in the appraisal of an instrument. Berry[4] attached great importance to the judgment of the patient; whereas, Bunch,[9] Fletcher,[10] Knudsen and Jones,[11] the

Ewings and Littler[12] and Regers[13] stressed more objective evaluation based upon thorough audiometric tests.

The amount of hearing loss has double significance both for the advisability of recommending an instrument and for the type of aid to be prescribed. Most authors were in agreement that cases with 30 to 40 decibel loss in the speech range require an aid only under unusual circumstances. In the range of 40 to 80 decibel loss the type of aid varies according to the shape of the audiometric curve. Fletcher[10] and Fowler[14] believed that if the aid were carefuly designed, all these cases could be satisfactorily fitted.

In cases of losses from 35 to 60 decibels Holmgren[2] favored the use of the vacuum tube aid and emphasized the fact that little amplification might be expected from a carbon aid where the loss extended above 2500 cycles per second. On the other hand, Day[15] believed that a carbon type would perform satisfactorily with losses from 35 to 60 decibels, although favoring a vacuum tube type above and below these limits.

In the fitting of cases of severe deafness most workers reported poor results. Berry[4, 20] anticipated slight improvement in cases where the loss ranged from 80 to 100 decibels. Fletcher,[10] Holmgren[2] and Kerridge[8] agreed that patients with losses greater than 110 decibels could not be helped.

Considerable disagreement appeared concerning the advisability of prescribing bone conduction instruments. Most workers felt, however, that low tone deafness could be assisted by such a unit. In these cases the high tones are filtered out by the skin and cranial bones and selective amplification of low tones is obtained. Bunch[9] and Hallpike,[16] nevertheless, believed that the value of bone conduction aids has been overemphasized and reported generally disappointing results. Kranz[17] and Berry[4] agreed that air conduction is of greater value in perception lesions, but the former believed that bone conduction yielded more satisfactory results in cases of mixed deafness. The Ewings and Littler[12] reported unfavorable results using a bone conduction unit with "practiced" cases of mixed and perception deafness.

PROCEDURE AND APPARATUS

In the design, construction and operation of electro-acoustic apparatus to be used in measuring hearing with and without a hearing aid, careful attention to the efficiency and the accuracy of equipment is essential.[18] The following is a description of the apparatus

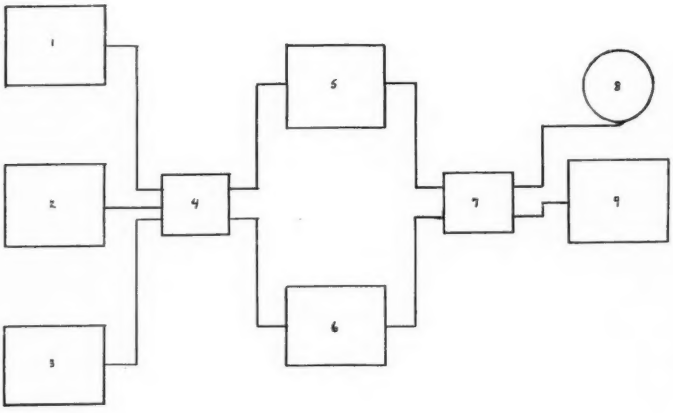


Fig. 1.—Diagram of apparatus—hearing aid clinic.

Legend:

Unit 1—WE 2A audiometer
Unit 2—ET reproducer
Unit 3—Microphone
Unit 4—Input selector switch
Matching equalizers
Unit 5—12 watt amplifier
Calibrated attenuation
Unit 6—30 watt amplifier
Calibrated attenuation
Unit 7—Output selector switch
Unit 8—Output volume indicator
Unit 9—Dual speaker system

used in the Hearing Aid Clinic of Central Institute for the Deaf (Fig. 1).

1. The Western Electric 2A Audiometer was selected as a pure tone source because it is battery operated, it has stable frequency calibration, it has no hum, and there is less than one per cent harmonic distortion. Although it uses a compensated oscillator, the compensation was measured electrically and suitable equalizers were inserted in the circuit, so that the over-all characteristics are essentially uniform. Because of the mechanical characteristics of the ear piece supplied with the instrument, a special coupling transformer was devised which provided suitable compensation.

2. A special 30-watt amplifier unit was designed and constructed to provide sufficient amplification plus reserve power with less than two per cent distortion, as measured with a General Radio noise and distortion meter. Its frequency characteristics are linear, plus or minus one decibel from 60 to 10,000 cycles per second.

3. An electrical transcription turntable which revolves at either 78.24 or 33⅓ revolutions per minute and a reproducer with a dual speed motor are used. The reproducer is of the crystal type, imposing a needle pressure of 35 grams, and is mounted on a broadcast type reproducer arm which will handle records up to 17 inches in diameter. The reproducer is connected to the amplifier through a special equalizer, which possesses mirror characteristics to those used in recording the special test electrical transcriptions. Inasmuch as the transcriptions used were recorded in the Central Institute laboratories under ideal conditions, recording and reproducing characteristics could be accurately measured.

4. A dual speaker system was arranged by mounting two concert-type Jensen electrodynamic speakers in an appropriately designed cabinet which has adequate baffling to provide uniform response to 50 cycles per second. This baffle cabinet is a felt-lined acoustic labyrinth which utilizes back pressure to reinforce frontal radiation in the proper phase. The direct current field supply is obtained from a unit which forms an integral part of the speaker system.

5. The volume level indicator consists of a Weston 01 MA Meter with an 8-inch dial. The rectifier is of the copper oxide type and the attenuator is a constant impedance H pad arrangement, eliminating any reflection which might introduce phase distortion.

6. Calibrated attenuation with two intensity controls is provided, one control for the pure tone test and the other for the sentence test, electrical transcription. Dial markings are indicated so that all tests made with this apparatus are uniform. All alternating current wiring has been installed in conduit with a single master switch, further simplifying operation.

7. Phonograph records were discarded in favor of electrical transcriptions since the frequency range of the latter is much wider, varying from 100 to 9,000 cycles per second as compared with 150 to 4,000 cycles per second for the average phonograph record. An electrical transcription of the type used for these tests has a background noise of less than 55 decibels below recorded level, which is 25 decibels less than the newest type phonograph record. The transcription has four separate tests on one side, each test consisting of 25 selected sentences, carefully enunciated at a constant voice level by a professional announcer. This feature eliminates the need for changing records during the test.

8. The chair in which the individual is seated during the tests is located so that the ears and hearing aid are two meters from, and at right angles to, the calculated points of the source of sound.

9. The laboratory which houses the special equipment was selected because of its acoustical properties and average residual noise level. Reverberation time (time required for a 1,000 cycles tone to attenuate 60 decibels or to 1/1,000,000 of its original value) is one second, and the noise level averages 35 decibels above absolute threshold.

CLINICAL PROCEDURE

The patient is first interviewed with particular attention to age, employment, children and previous use of hearing aids. The consulting otologist then records the complete anamnesis. In order to determine the exact loss by bone and air conduction in each ear, the first step in actual testing is the pure tone audiometer test using both air and bone conduction receivers. These tests are carried out in a relatively quiet room. The patient is then tested with the apparatus previously described in a room with reverberation characteristics which simulate those of the average living room. The pure tone and sentence tests employing the loud speaker are then administered to the unaided ears. The test is repeated using the hearing aids to be evaluated. After the amount of improvement with each aid is recorded and studied, recommendation is made which favors the aid or aids exhibiting the most satisfactory characteristics in terms of the patient's responses.

At all sessions of the clinic a qualified educator of the hard of hearing, familiar with the psychological and pedagogical problems faced by those with impaired hearing, is available for consultation. It is his function to make recommendations for lip reading and acoustic training after the aid has been purchased, since this type of education is necessary if optimum benefit is to be derived from the use of the instrument. The personnel of the clinic thus includes a consulting otologist, trained audiometrists, an acoustic engineer and an educator of the hard of hearing.

RESULTS

The results of this investigation lend themselves to convenient presentation if they are considered according to the following classifications of impaired hearing:

1. Conduction deafness is characterized by normal or slightly decreased bone conduction, negative Rinne and a normal or retracted tympanic membrane. Many of these cases are classical examples of otosclerosis while the remainder are diagnosed as hyperplastic otitis media.

2. Mixed deafness is characterized by early perceptive lesions in association with middle ear disease.

3. Perception (nerve) deafness is characterized by a marked reduction in air and bone conduction.

Of more than 100 cases examined during the period of operation of the clinic, 75 unselected cases are reported. Of these, 19 were found to be conduction deafness, 29 mixed deafness, and 17 perception deafness. The results in 10 cases showed a loss greater than 110 decibels in the speech range and no attempt was made to prescribe an instrument.

Thirteen different aids, most of which have been accepted by the Council of Physical Therapy of the American Medical Association,[19] including various models produced by seven manufacturers, were available to the clinic for evaluation. The instruments mentioned in the present report are designated by letters of the alphabet with subnumerals indicating different models of the same manufacturer. A sampling of ten cases from each category of deafness is reported in detail. Inspection of Tables 1, 2, and 3 indicates that certain aids were used more frequently than others. This was due to the greater availability of these particular instruments.

Conduction Deafness. Examination of the cases of conduction deafness in Table 1 indicates that a maximum improvement of 30 decibels at various crucial frequencies was obtained. Only in isolated instances, in each case limited to a single frequency, was a greater improvement demonstrated. It is evident that individual instruments vary widely in performance. In many cases comparison was made between the aid worn by the patient when he came to the clinic and the instruments which were permanently available. An example of the striking contrast between two instruments can be noted in cases No. 2 and No. 3 where aids A2 and F2 were appraised.

Consistently superior performance was observed not only in the amount of amplification, but also in the range of frequencies amplified where aid A2, with a bone conduction unit, was used. Different instruments varied with regard to the frequency at which maximum amplification was obtained. Instruments B1 and B2 showed con-

sistent "peaking" at 1024 cycles per second and aid F2 seemed to achieve greatest amplification at 2048 cycles per second.

Mixed Deafness. Examination of Table 2 indicates that in cases of mixed deafness, a generally uniform gain of from 25 to 35 decibels was noted with occasional gains of from 35 to 45 decibels at single frequencies. Most of the instruments yielded improvement in the frequencies from 256 to 4096 cycles per second with an occasional exception, as case No. 1, using aid A1, and case No. 2, using aid E2, illustrate. Variability in performance by the same instrument in different cases of the same type of deafness was observed. For example, aid A1 in case No. 1 yielded no gain but the same instrument used in case No. 4 provided substantial amplification. In cases where bone conduction units were tested appreciable gains in the range from 256 to 2048 cycles per second were noted. No significant increase in amplification with these units was observed at 4096 cycles per second. Aid A1, an air conduction instrument, showed consistent "peaking" from 1024 to 2048 cycles per second.

Perception Deafness. In the cases of perception deafness shown in Table 3 a maximum amplification of from 30 to 35 decibels, restricted in most instances to the range from 256 to 512 cycles per second, was obtained. In the remaining frequencies little amplification was observed, although beneficial results prevailed in some instances, e.g., cases No. 5, using aid B2, and No. 6, using aids A1 and B1. No consistent "peaking" was observed.

The evaluation of aids on the basis of responses to the pure tone audiometer was supplemented by appropriately selected sentence tests in most of the cases (Table 4). It was significant that in some cases a gain of only 10 decibels throughout the range from 256 to 2048 cycles per second yielded from 25 to 50 per cent increase in sentence intelligibility. In the few instances where bone conduction units were evaluated by the sentence tests, a beneficial increase in intelligibility was observed (as in case No. 2, using aids A2 and B2). In two instances where there was lack of response to the sentence test with the unaided ear, there was from 48 to 100 per cent improvement with the instrument. Additional data concerning the appraisal of hearing aids by means of the sentence intelligibility technique are being gathered.

DISCUSSION

The functioning of the Hearing Aid Clinic at Central Institute for the Deaf demonstrates the possibility of evaluating hearing aids scientifically and impartially in a clinical atmosphere. Although the

limitations of clinical operation preclude the possibility of testing every aid with every patient, multiple testing is being carried on in selected cases, the results of which will be reported in a subsequent publication.

Although the usual air and bone conduction audiometric tests are made under relatively quiet conditions, the room in which the hearing aid evaluation takes place simulates average living room acoustical conditions, both as to noise level and reverberation characteristics. True appraisal of an instrument can be made only under such conditions.

The patient's subjective judgment as to the advisability of a particular aid is either corroborated or altered by the objective character of the intelligibility and audiometric tests. Hence, because of the availability of facts presented without prejudice, psychological resistance to an instrument is reduced to a minimum. The amount of amplification obtained in fitting aids varies with the type of deafness involved. Cases of conductive deafness presented comparatively little difficulty in fitting, and, although the maximum improvement in most cases was limited to 30 decibels, the gains occurred at those frequencies necessary for optimum intelligibility of speech.

Optimum results were observed in cases of mixed deafness with consistent improvement of from 25 to 35 decibels. Although this amount of improvement is less than that noted in cases of perception deafness, the amplification was spread over a wide frequency range, while in the latter group the improvement was restricted to a very narrow portion of the lower frequency band. Amplification of extraneous noises which dominate the lower portion of the frequency spectrum results in the masking of those tones, the hearing of which is essential for intelligibility of speech. Although some instruments are purportedly constructed for the suppression of these low tones, in practice their performance fails to measure up to the claims of the manufacturers. The problem of successfully fitting cases of perception deafness remains a challenging one.

It is important to note that in many cases a slight gain in amplification through the use of a hearing aid, as recorded on the pure tone test, results in a greater proportionate improvement on the sentence intelligibility test. This undoubtedly occurs because enough gaps in the auditory pattern are filled to enable the patient to bring into play his ability to synthesize the language stimulus into a meaningful whole. It is possible, therefore, that a gain of as little as 10 decibels may be sufficient to bridge the gap between intelligibility

and unintelligibility of speech. The need for the development of the ability to integrate auditory language stimuli emphasizes the importance of a period of acoustic training for those who are in the process of adjusting to a newly acquired hearing aid.

SUMMARY

1. Specially designed equipment and a clinical procedure for evaluating hearing aids impartially and scientifically are described.

2. The desirability for cooperation among the consulting otologist, the acoustic engineer, the educator of the hard of hearing and the hearing aid manufacturer is emphasized.

3. An unselected series of cases of impaired hearing, classified according to type of deafness, was examined and tested for hearing aids in the clinic.

4. Thirteen different hearing aids, including various models produced by seven manufacturers, were evaluated.

5. Results may vary according to the instrument tested, according to the type of deafness, and within any category of deafness.

6. In cases of conduction deafness a maximum improvement of 30 decibels in the speech range is reported. Bone conduction units are superior in some instances and air conduction aids are better in others. The results do not warrant a generalization as to the type of aid to be prescribed in these cases.

7. In cases of mixed deafness a general gain of 25 to 35 decibels in the speech range is noted. Optimum results are indicated for this type of deafness.

8. In cases of perception deafness a maximum improvement of 25 to 35 decibels within a limited frequency range is observed. Cases of extreme deafness cannot be fitted adequately with a hearing aid and they remain a challenging problem.

9. A slight increase in hearing with an aid as measured by a pure tone test may result in a greater proportionate increase in intelligibility. This is due to the fact that gaps in the auditory pattern are filled, facilitating synthesis of auditory language stimuli.

10. A period of acoustic training is desirable after the acquisition of a hearing aid.

The authors wish to acknowledge the technical assistance of Mr. Alfred Thea, Miss Elizabeth Gorsuch and Miss Meredith Smith.

818 S. KINGSHIGHWAY

BIBLIOGRAPHY

1. Halsted, T. H. and Grossman, F. M.: Some Problems Involved in the Fitting of Hearing Aaids, New York State J. Med. 41:352, 1941.

2. Holmgren, L.: Hearing Tests and Hearing Aids, a Clinical and Experimental Study, Acta Otolaryng., Supplement 34, 1939.

3. Senturia, B. H. and Thea, Alfred: Bone Conduction—A Preliminary Study, Laryngoscope 52:673, 1942.

4. Berry, G.: The Use and Effectiveness of Hearing Aids, Laryngoscope 49:912 (Oct.), 1939.

5. Ewing, A. W. G. and Ewing, I. R.: The Handicap of Deafness, New York, Longmans, 1938.

6. Sabine, P. E.: Acceptance Tests of Hearing Aids, J. A. M. A. 115:1633 (Nov.), 1940.

7. Knudsen, V. O.: An Ear to the Future, J. Acous. Soc. of Amer. 1:29 (July), 1939.

8. Kerridge, P.: Administration of Hearing Aid Clinic, J. Laryng. and Otol. 53:370, 1938.

9. Bunch, C. C.: Hearing Aids, Trans. Am. Acad. of Ophth. and Otol., March-April 1942, p. 163.

10. Fletcher, H.: Can We Scientifically Advise Patients as to the Effectiveness of Hearing Aids? ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 41:727, 1932.

11. Knudsen, V. O., and Jones, I. H.: Studies of the VIIIth Nerve by the Research Study Club of Los Angeles, St. Louis, The Laryngoscope Press, 1937.

12. Ewing, A. W. G., Ewing, I. R. and Littler, T. S.: The Use of Hearing Aids, London Medical Research Committee, Special Report No. 219, 1936.

13. Reger, S.: Personal Communication.

14. Fowler, E. P.: The Use of Threshold and Louder Sounds in Clinical Diagnosis and the Prescribing of Hearing Aids, Trans. Am. Otol. Soc. 48:154, 1938.

15. Day, K. M.: Discussion. Arch. Phys. Ther. 22:100 (Feb.), 1941.

16. Hallpike, C. S.: Hearing Aids and Hearing Tests, J. Laryng. and Otol. 49:240, 1934.

17. Kranz, F. W.: Hearing Aids, Sonotone Corporation, May, 1940.

18. Standards of Electroacoustics, Institute of Radio Engineers, Inc., New York, N. Y., 1938.

19. McFarlan, D.: Hearing Aids Accepted by the Council on Physical Therapy, Am. Med. Ass. 36:240, 1942.

20. Berry, G.: Hearing and Hearing Aids—A Review of the Recent Literature, Laryngoscope 52:143, 1942.

TABLE 1

CONDUCTION DEAFNESS

Case	Instrument	Type	Gain in Decibels at Specific Frequencies				
			256 c.p.s.	512 c.p.s.	1024 c.p.s.	2048 c.p.s.	4096 c.p.s.
1.	A 1	Air	10	15	10	10	10
	B 1	Air	20	15	35	−5	10
2.	A 2	Bone	30	10	20	25	20
	F 2	Bone	15	0	−5	25	15
3.	F 2	Bone	0	−5	−5	10	0
	A 2	Bone	30	15	25	25	25
4.	A 2	Bone	5	15	15	5	0
	B 1	Air	5	5	20	10	0
	B 2	Air	5	10	20	10	20
5.	A 1	Air	10	20	20	20	20
	B 2	Air	0	5	10	5	10
6.	A 2	Bone	20	25	30	15	5
	A 1	Air	10	10	20	20	5
7.	A 1	Air	10	15	5	5	0
	A 2	Bone	15	15	5	5	0
8.	A 1	Air	0	20	10	35	5
	F 1	Air	5	10	15	20	10
9.	A 2	Bone	−5	10	20	10	0
	A 1	Air	0	0	25	15	15
10.	B 1	Air	10	20	30	10	5

c.p.s. Cycles per second.

− Loss in amplification with instrument.

TABLE 2

MIXED DEAFNESS

Case	Instrument	Type	Gain in Decibels at Specific Frequencies 256 c.p.s.	512 c.p.s.	1024 c.p.s.	2048 c.p.s.	4096 c.p.s.
1.	A 1	Air	−10	0	0	−5	−5
2.	A 1	Air	15	10	30	20	0
	E 2	Air	0	5	10	−5	−20
3.	A 1	Air	5	10	15	20	5
	C 1	Air	5	15	10	20	5
4.	D 1	Air	25	20	15	20	10
	A 1	Air	35	15	40	45	30
5	A 2	Bone	20	20	30	30	0
	C 2	Bone	25	25	30	30	0
6.	B 2	Air	5	10	20	25	5
	A 1	Air	20	20	20	30	15
7.	B 1	Air	0	0	10	20	15
	A 1	Air	35	30	25	15	15
8.	F 2	Bone	10	15	0	10	0
	A 2	Bone	20	20	15	30	5
9.	D 1	Air	10	30	35	10	0
	A 1	Air	10	30	20	15	0
10.	A 1	Air	−5	5	20	20	0
	F 1	Air	0	−5	5	0	0

c.p.s. Cycles per second.

− Loss in amplification with instrument.

TABLE 3

PERCEPTION DEAFNESS

Case	Instrument	Type	Gain in Decibels at Specific Frequencies				
			256 c.p.s.	512 c.p.s.	1024 c.p.s.	2048 c.p.s.	4096 c.p.s.
1.	A 1	Air	0	5	0	10	–20
2.	A 1	Air	0	15	5	0	–5
3.	A 1	Air	25	10	15	15	NR
4.	G 1	Air	30	25	NR	NR	NR
	A 1	Air	35	35	NR	NR	NR
5.	D 1	Air	30	15	20	–15	5
	A 1	Air	20	15	10	–5	0
	B 2	Air	25	30	30	10	5
6.	B 1	Air	–5	–5	30	20	15
	A 1	Air	–5	0	50	10	20
	B 3	Air	–15	–20	10	0	–15
7.	A 1	Air	0	10	NR	NR	NR
8.	A 1	Air	–5	10	5	25	10
	A 3	Air	5	5	5	NR	NR
9.	A 1	Air	5	15	15	NR	NR
10.	A 1	Air	5	10	25	0	0

c.p.s. Cycles per second.

NR No response with instrument.

– Loss in amplification with instrument.

TABLE 4

COMPARATIVE GAIN WITH HEARING AID ON PURE TONE AND INTELLIGIBILITY TESTS

Case	Instrument	Type	Type of Deafness	Gain in Decibels at Specific Frequencies			Percentage Improvement of Intelligibility Sentences	
				512 c.p.s.	1024 c.p.s.	2048 c.p.s.	Without Aid	With Aid
1.	G 1	Air	Conductive	20	20	10	44	84
2.	A 2	Bone	Conductive	15	15	5	52	88
	B 1	Air	Conductive	5	20	10	N.T.	84
	B 2	Bone	Conductive	10	20	10	44	84
3.	A 1	Air	Conductive	10	5	5	52	76
4.	A 1	Air	Mixed	10	5	5	84	100
5.	A 1	Air	Perceptive	10	10	25	60	100
6.	A 1	Air	Mixed	10	30	20	NT	83
	E 2	Air	Mixed	5	10	−5	NT	46
7.	D 1	Air	Mixed	20	15	20	0	0
	A 1	Air	Mixed	15	40	45	0	48
8.	A 1	Air	Mixed	20	30	30	0	96
	C 2	Bone	Mixed	25	30	30	0	100
9.	A 1	Air	Conductive	20	20	10	76	100
	B 2	Air	Conductive	5	10	5	N.T.	N.T.
10.	A 2	Bone	Conductive	5	20	25	60	96

c.p.s. Cycles per second
NT No test performed.

XII

CANCER OF THE NASOPHARYNX*

CHARLES L. MARTIN, M.D.

DALLAS, TEXAS

Cancer of the nasopharynx originates most frequently in the pharyngeal tonsil and the fossae of Rosenmüller and much less often in the periphery of the choanae and the posterior nasopharyngeal wall. Some authors have described such tumors extending downwards from the sphenoid sinuses and even from the pituitary fossa and Furstenberg[1] reported a case with the point of origin completely within the eustachian tube. Since the detection of small tumors in these regions requires considerable skill, it is not surprising that so many of them are overlooked in clinical practice.

However, the large number that are incorrectly diagnosed after secondary invasion occurs seems inexcusable and indicates that many otolaryngologists are unfamiliar with the rather complex clinical picture which they may produce. Woltman[2] states that only one of the 25 cases examined at the Mayo Clinic prior to 1922 had been correctly diagnosed and New[3] observed that 185 operations for conditions other than cancer of the pharynx had been carried out in a series of 194 cases reported in 1931. Some of the erroneous diagnoses listed by Woltman were: tonsillitis, diseased teeth, sinus disease, trifacial neuralgia, nasal polyps, deflected septum, otitis media, pharyngeal abscess, Hodgkin's disease, mumps, pituitary tumor, demential paralytica and syphilis. Although Jackson[4] published a résumé of the French, German and Italian literature on the subject in the Journal of the American Medical Association in 1901, Needles,[5] as recently as 1937, described unnecessary operations performed on 12 of 35 patients with cancer of the nasopharynx in a New York hospital.

PATHOLOGY

Pathologists find the exact classification of the various types of cancer encountered in the nasopharynx rather difficult and tend to differ among themselves. However, radiologists are interested primarily in the determination of radiosensitivity rather than terminol-

*Presented before the Texas Ophthalmological and Otolaryngological Society.

ogy. Experience has shown that undifferentiated epitheliomas, lympho-epitheliomas, lymphosarcomas and plasmocytomas respond satisfactorily to doses of irradiation which are well tolerated by the normal tissues, whereas adenocarcinomas, well-differentiated epitheliomas, the spindle cell carcinomas described by Martin and Stewart[6] and the more differentiated chordomas respond poorly to the same doses. Fortunately approximately 85 per cent of all such tumors encountered in practice fall into the first group. At the Memorial Hospital in New York it is customary to designate the less differentiated tumors of epithelial origin as transitional cell carcinomas, a terminology suggested by Quick and Cutler,[7] while at the Mayo Clinic all epithelial neoplasms are divided into the four classes recommended by Broders. Adenocarcinomas of gland origin in the nasopharynx are called cylindromas by Dr. A. P. Stout of the Presbyterian Hospital in New York but the pathologists at the Memorial Hospital refer to them as malignant tumors of the salivary glands from which they undoubtedly arise. Lympho-epitheliomas as described by Schmincke[8] can easily be confused with lymphosarcomas and transitional cell carcinomas but, since all of these three conditions are radiosensitive, their differentiation is of no great practical importance. Although the author has never seen a sarcoma of the nasopharynx, Martin and Blady[9] state that they have observed one case of myxosarcoma. They make no comment relative to its response to irradiation. Chordomas are thought to be radioresistant and most of them are, but one such tumor showing relatively poor cell differentiation was treated successfully in our Clinic. Perhaps mixed tumors should not be included in a paper on cancer of the nasopharynx but complete destruction of the soft palate and both sphenoids resulted from such a tumor in one of our patients and the symptoms were as disabling as any observed with true cancer. Long remissions followed irradiation therapy but multiple recurrences were observed during seven years of treatment.

LOCAL GROWTH

Although the development of the primary tumor produces such symptoms as nasal obstruction, epistaxis, nasal discharge, chronic sore throat, postnasal pain, dysphagia and the sensation of a lump in the throat, the manifestations of the disease which first bring the patient to a physician are more often those due to secondary extension. New observed that only about half of his large group complained of symptoms produced by the primary growth and only 6 of Needle's 35 patients had any such manifestations early.

Local soft tissue extension soon produces a blockage of the eustachian tube, and deafness, tinnitus, a feeling of stuffiness in the ears, retraction of the drum and otitis media may result. In some instances the growth extends outward within the eustachian tube, perforates the tympanic membrane and fills the external auditory canal. A biopsy was easily carried out on a bleeding mass of friable tissue seen protruding from the external ear in one of our patients. An anterior displacement of the anterior pillar on the affected side and invasion of the soft palate are occasionally observed. When the pterygoid and masseter muscles are invaded the victim can open the mouth very little, if at all.

INTRACRANIAL EXTENSION

The symptoms which are most confusing to the examiner result from the extension of the tumor into the cranial cavity. This complication has been observed in about one-third of the patients suffering from cancer of the nasopharynx and should always be kept in mind as a possible development, even though it cannot be demonstrated.

Much difference of opinion has arisen concerning the exact pathway followed by this extension of the disease. Martin and Blady contend that the tumor passes directly upwards through the foramen lacerum, which lies about one centimeter from the fossa of Rosenmüller, and report a case with involvement of several cranial nerves showing no roentgenographically demonstrable defect in the base of the skull. Reverchon,[10] Collet and Rebattu[11] and Gaillard[12] proposed the same explanation based on autopsy findings many years ago. The author[13] published roentgenograms of the skull made in the vertical position demonstrating bone destruction produced in the middle fossa by these invading neoplasms in 1939 and stated that the sphenoid bone was invaded by tumor tissue. In 1924, Barre and Stoeber[14] demonstrated actual invasion of the sphenoids and ethmoids in vertical sections of skulls of patients dying of the disease and Bach, Lederer and Palevsky[15] have recently reported careful postmortem findings in a patient having invasion of both sphenoids and the roof of the epipharynx. An autopsy performed on one of our own advanced cases showed the middle fossa to be so completely invaded that it fell apart during the examination. Our experience leads us to believe that both processes may occur. In some instances the tumor passes upwards through the foramen lacerum and then slowly enlarges this opening in all directions. In others, direct invasion produces destruction of all of the bony structures making up

the roof of the pharynx. Careful x-ray studies of the skull made in the vertical and lateral positions should be carried out in all patients with this disease. In a series of 40 cases recently reported by Lenz[16] bone involvement was demonstrated in the body of the sphenoid in 10, the greater wing of the sphenoid (mesial margin) in 12, the petrous tip in 10, the basi-occiput in 8, the foramen ovale and spinosum in 5, the posterior margin of the vomer in 3 and the sella turcica in 3.

Regardless of the mechanism of the bone destruction the neoplasm enters the cranial vault just lateral to the sella turcica in the region of the foramen lacerum and may extend either anteriorly or posteriorly. The dura is pushed upwards but practically never invaded. Although the pituitary gland may be pushed out of the sella turcica and the posterior horns be completely destroyed, no dysfunction of the gland has been observed. Extension forward through the sphenoid fissure into the orbit sometimes produces exophthalmus and upward and backward extension can bring about the involvement of one intracranial nerve after another. A vertical section cut through the middle fossa shows the nerves to be placed in the following order if one reads from below upwards: abducens, branches of the trigeminus, oculomotor, trochlear, and optic. A study of Table 1, which gives the incidence of nerve involvement in 234 patients studied by five clinicians, shows as would be expected that the occurrence of nerve symptoms due to extension of the tumor into the middle fossa follows this same order. As will be explained later, the posterior cranial nerves are likely to be compressed by extracranial, rather than by intracranial, metastases. It is interesting to note that auditory nerve symptoms practically never occur. This is logical because the auditory nerve enters the temporal bone almost immediately after leaving the brain through a foramen located well behind the petrous ridge, where it is protected from tumor tissue growing backwards from the middle fossa. A study of Table 1 shows why the patient with early intracranial extension usually complains of double vision from internal strabismus, and pain or anesthesia in the face, the nose or the teeth.

LYMPH NODE INVOLVEMENT

Enlarged cervical lymph nodes occur sooner or later in practically all cases and constituted the first clinical symptoms observed by the patient in 42 per cent of New's 194 patients. Needles observed such enlarged glands in 25 of his 35 patients, while the incidence at admission was reported as 80 per cent by Salinger and

TABLE 1

CRANIAL NERVES INVOLVED

Author	Cases	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Woltman	79	0	5	4	4	17	18	1	0	6	3	3	5
Furstenberg	40	0	2	4	4	5	8	3	1	1	1	0	1
Hansel	17	0	3	4	3	4	5	2	0	3	3	3	4
Needles	35	2	2	8	5	10	14	2	0	4	3	4	4
Lenz	63	0	3	3	2	16	12	3	0	10	10	1	8
	234	2	15	23	18	52	57	11	1	24	20	11	22

Pearlman[17] and 77 per cent by Martin and Blady. Those first observed lie in the deep cervical region below the tip of the mastoid and beneath the upper portion of the sternomastoid muscle. Late dissemination occurs in the posterior cervical chain and occasionally the submaxillary and submental glands are involved. Although enlarged nodes are usually seen first on the side occupied by the tumor, they eventually become palpable on both sides of the neck. A bulging of the posterior pharyngeal wall suggests metastases in the retropharyngeal nodes which lie just above the level of the palatine tonsil.

Compression of the glossopharyngeal, the vagus and the spinal accessory nerves high in the neck, resulting from the expansion of glands situated between the cervical spine and the mastoid, may produce the jugular foramen syndrome characterized by nasal regurgitation of fluids, dysphagia of solids and hoarseness. Since the hypoglossal nerve and the sympathetic chain lie in this same region, a deviation of the tongue and Horner's syndrome can result from the same type of metastases. It is the author's opinion that such symptoms are more frequently produced from extracranial than from intracranial extension. In some instances pressure on the seventh nerve near its point of exit beneath the mastoid brings about a facial paralysis.

GENERALIZED METASTASES

Extension below the clavicles often occurs fairly rapidly and in many instances patients who have shown a complete regression of the manifestations of the disease in the pharynx and the neck following irradiation return in a few months complaining of a nonproductive cough, pain in the chest and loss of weight produced by metastatic lesions in the mediastinal lymph nodes and adjoining pulmonary structures. Although the intrathoracic tumors can be controlled by x-ray therapy, no such patient in our series has obtained a cure because generalized metastases are invariably established by the time the pulmonary symptoms appear. Such metastases appear in the bones, the liver, the kidneys, the spleen and the retroperitoneal lymph nodes and produce the type of death observed with other types of disseminated malignant disease.

TREATMENT

Surgery has accomplished relatively little in the treatment of cancer of the nasopharynx and many good otolaryngologists have adopted the gloomy attitude of Furstenberg who states, "The prognosis

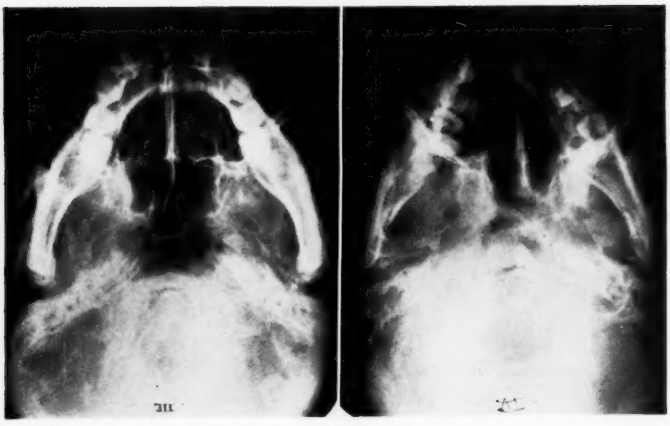


Fig. 1.—Roentgenograms of the skull made in the vertical position contrasting a normal skull (left) with the skull of a patient dying from an advanced transitional cell carcinoma which had invaded the floor of the middle fossa, the sella turcica and the posterior portions of the sphenoids.

remains hopelessly futile." However, the picture has changed since the divided dose method of administering x-ray therapy advocated by Coutard[18] came into general use some ten years ago. He was able to report 10 percent of 89 patients treated prior to 1926 as well at the end of five years even though his technic had not been perfected. More recently Martin and Blady have obtained 25 per cent of five year cures in a series of 80 patients and Lenz has reported 27.6 per cent of 44 patients symptom-free after five years of observation. All of these patients received irradiation therapy alone and each series includes all of the patients treated regardless of the stage of the disease.

These promising results are based on the fact that approximately 85 per cent of the primary lesions observed in practice are so radiosensitive that they can be completely eradicated by doses of irradiation which produce no irreparable damage to the normal tissues. It is true that such therapy sets up painful reactions in the mucous membranes and the skin of the treated areas but these reactions heal in two or three weeks and are relatively insignificant when compared with the results obtained. The details of the technic used by the author and the clinical care of the patients receiving treatment have been discussed in previous papers[19, 20] and will not be repeated here.

American radiologists have attempted to improve the original French technic and as a result the plan of treatment varies in different treatment centers. Differences of opinion arise principally over whether x-ray therapy should be augmented by pharyngeal radium applications and over the size and location of portals used in x-ray therapy. From a review of our own cases conducted in 1939 we observed that many of our failures resulted from the appearance of metastases in the mediastinum or the intracranial cavity four to six months after the disappearance of all evidence of the disease in the pharynx and the cervical region. In many instances no such metastases could be detected at the original visit. It was also noted that no patient recovered after lesions appeared in the mediastinum, and that generalized metastases could be expected even when the treatment of the mediastinum was successful. These findings led us to believe that more cures might be obtained by administering additional irradiation to the base of the skull and thorax in the early cases. The following improvements in technic were then adopted:

1. Areas laid out over each side of the pharynx should extend from the lateral wall of the orbit to a point one-half inch behind the mastoid and should include the base of the skull and the submental area as well as the upper portions of the triangles of the neck. The total dosage given to each area during a period of three and a half weeks averages 3200 roentgens measured in air and should rarely exceed this amount.

2. When the reaction from this series has subsided, a third area of similar size laid out over the base of the occipital region and the back of the neck should receive 3000 roentgens at the rate of 300 roentgens per day.

3. At, or about, the same time 2400 roentgens should be delivered through 15 cm. portals to the front and back of the upper mediastinum at the rate of 300 roentgens per day in an effort to forestall downward extension through the lymphatics in this region.

Martin and Blady, who augment their relatively inefficient method of irradiating the pharynx through small portals laid out over the cheeks by intra-oral x-ray therapy and intrapharyngeal radium applicators, take exception to the plan detailed above, claiming that the reactions produced with such large portals are too severe. As a matter of fact the dosage actually delivered to the pharynx is not as large as that advocated by these authors and the complicated precautions which they use to protect the eyes and tongue are rendered unnecessary. No untoward sequelae have followed the

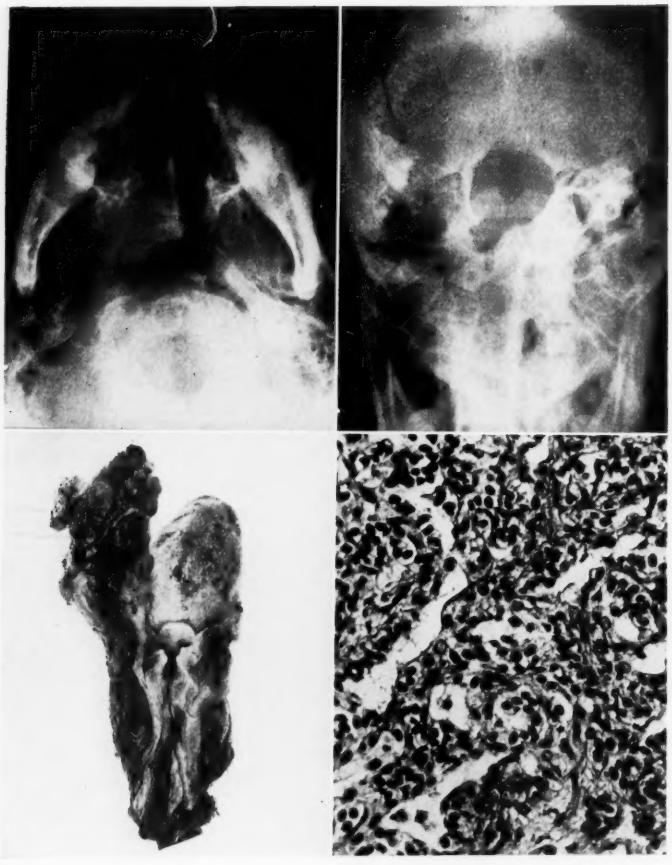


Fig. 2.—Roentgenograms and pathological material from a patient dying with an advanced transitional cell carcinoma of the pharynx which had extended through the floor of the middle fossa on the affected side, destroyed the inner petrous portion of the temporal bone and protruded through the external auditory canal.

procedure and, although no five year statistics are yet available, the results observed in a small group of patients have been encouraging. In the author's opinion the technic of Martin and Blady, designed to deliver larger doses to smaller areas, should be reserved for the more radioresistant tumors when they are well localized. Their success with a squamous cell carcinoma, grade I, covering the posterior and lateral walls of the pharynx and the upper surface of the soft palate and associated with a marked ozena, emphasizes the value of their combined x-ray and radium method in a slowly metastasizing, very resistant neoplasm. A similar case complicated by extensive intracranial involvement treated over larger areas in our clinic showed a poor response and succumbed to the disease.

The following case histories illustrate some interesting points referred to in the paper:

CASE 1.—Mrs. A. R. C., a white woman 22 years of age, entered our clinic on April 20, 1937. A diagnosis of transitional cell carcinoma of the pharynx was made in another clinic six months previously and a series of 20 x-ray treatments directed at the pharynx through small portals had been given. At the time that this therapy was started she complained of pain about the right eye, double vision, a swollen right jaw, inability to open her mouth and a bloody nasal discharge. The discharge ceased but the other symptoms persisted and at admission she was found to have photophobia, an internal strabismus on the right side, a tingling in the right side of the face and a small mass of greyish tissue in the right fossa of Rosenmüller, biopsies of which revealed no malignant tissue. Roentgenograms of the skull made in the vertical position showed a rounded area of destruction measuring one inch in diameter in the middle fossa just to the right of the sella turcica and surrounding the tip of the petrous portion of the temporal bone which was partially destroyed.

Portals measuring 10 x 15 cm. were laid out over both sides of the skull so as to include the middle fossa and the entire pharynx. Daily doses of 300 roentgens measured in air and generated at 220 Kv. peak with a filter of 0.8 mm. of tin, 0.25 mm. of copper and 1.0 mm. of aluminum at a target skin distance of 50 cm. were administered alternately to the two portals until each had received a total of 3000 roentgens.

Her symptoms showed much improvement but she returned on Nov. 20, 1937, complaining of dizziness and a rather unsteady gait. She then received 300 roentgens daily directed through a portal measuring 10 x 15 cm., laid out over the lower occipital region and posterior neck, until 3000 roentgens had been given. The treatment factors were identical with those used in the first series.

She returned on June 20, 1938, stating that she had gained a total of 30 pounds, had normal vision and was free of all symptoms. No muscle weakness could be detected and the strabismus was no longer evident.

She has had two normal pregnancies since she was treated and has remained well for almost six years.

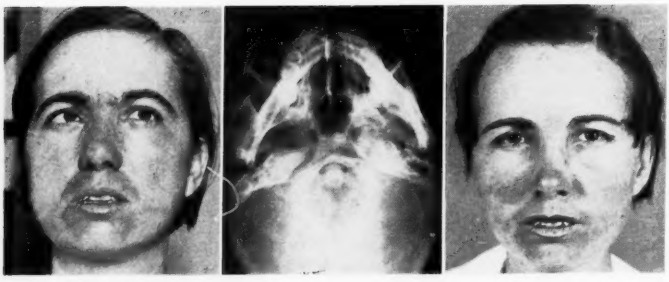


Fig. 3.—Photographs made before and after x-ray therapy and a vertical roentgenogram showing a large defect in the right middle fossa produced by a transitional carcinoma of the pharynx in Case 1. The strabismus disappeared soon after she was treated and she has remained well for almost six years.

Case 2.—Mrs. L. M. C., a white woman 25 years of age, entered our clinic on Feb. 24, 1941. For six months she had complained of severe headaches often accompanied by nausea and for three months she had noticed a right-sided deafness and some swelling of the right cheek. Soon after the deafness appeared she developed double vision and pain in the right side of the face. On Feb. 1, 1941, she consulted a competent otolaryngologist who made a diagnosis of chronic infection of the right antrum. This diagnosis was confirmed by a set of roentgenograms made in the conventional manner. A radical operation was performed but her symptoms slowly became worse and the correct diagnosis was suggested two weeks later by a neurological consultant. Her appetite had been poor and she had lost a total of 25 pounds since the onset of her illness.

At admission she was poorly nourished and very uncomfortable. The external rectus of the right eye was completely paralyzed and there was a loss of sensation in the right cheek. There was a hard lymph node measuring three-fourths inch in diameter in the right submaxillary region but no other glands could be felt in the neck. A mass of tumor tissue seen high up in the right posterior nasopharynx entered the fossa of Rosenmüller. A biopsy was reported as epidermoid carcinoma, grade IV. Roentgenograms of the skull showed increased density throughout the right antrum and both ethmoids secondary to infection and an area of decreased density measuring five-eighths inch in diameter in the right middle fossa in the region of the foramen lacerum. A roentgenogram of the chest revealed no evidence in intrathoracic extension.

The x-ray therapy was identical with that given to Case 1 except that two doses of 300 roentgens were given through a round portal 7 cm. in diameter laid out over the right cheek and no treatment was administered to the occipital region. The amount of irradiation was kept to a minimum because of her poor general

condition which necessitated the repeated intravenous use of glucose and thiamin chloride and intramuscular injections of liver extract.

On April 16, 1941, she was much improved. The strabismus had completely disappeared and the pharynx had a normal appearance. Her only symptoms were slight deafness in the right ear and the dryness of the mouth noted by all such patients. On Feb. 13, 1942, she had gained back most of her weight and felt quite well except for an occasional blockage of the right eustachian tube. She has continued to feel well and has remained free of all evidence of her pharyngeal neoplasm for a period of two years.

CASE 3.—Mrs. A. B. A., a white woman 42 years of age, entered our clinic on March 4, 1942. She had been treated for chronic sinusitis for 20 years and ozena for 8 years. For two months she had complained of pain in the frontal and both maxillary areas with intermittent blockage of the nasal passages. Microscopic study of tissue removed from the nasopharynx revealed squamous cell carcinoma, grade I. A tumor filling the nasopharynx and the posterior left nasal passage with involvement of the posterior portion of the nasal septum was reported. Roentgenograms of the skull showed increased density in both antra and both ethmoids from an old infectious process and complete destruction of both sphenoids and the posterior horns of the sella turcica from tumor invasion. She had a right-sided exophthalmus and swelling of the lids secondary to direct extension of tumor tissue into the orbit.

During the week beginning March 3, 1942, small heavily filtered radium capsules were placed in each side of the nasopharynx and weak radium needles were inserted into the posterior nasal passages. The total dose given in this way was 945 mg. hrs. During this same period a total of 1575 roentgens was administered through the cheeks. On April 23, 1942, portals measuring 10 x 15 cm. were laid out over each side of the skull so as to include the middle fossa and the pharynx, and a total of 3150 roentgens was given to each area during a period of 22 days with the treatment factors described for Case 1. On June 16, 1942, a 7 cm. circular portal was laid out over the frontal region and 2520 roentgens were directed downward towards the sphenoids during a period of 9 days. During an 11-day period beginning July 8, 1942, a total of 3150 roentgens was given through an occipital portal measuring 10 x 10 cm.

She showed some temporary improvement during the first two months of treatment but slowly became worse and died with a terminal pneumonia on July 31, 1942.

This patient had a very radioresistant tumor and the amount of irradiation given was not large enough to control it. It seems unlikely that adequate treatment could have been safely administered to such an extensive neoplasm but the technic of Martin and Blady might have been successful earlier in the course of the disease.

CASE 4.—Mrs. O. C. W., a white woman 35 years of age, entered our clinic on March 4, 1942. For many years she had complained of a nasal discharge and repeated colds attributable to sinus disease. In September, 1941, she first noticed some nasal obstruction accompanied at intervals by a bloody nasal discharge. About one month before admission she consulted a doctor because of deafness and tinnitus.

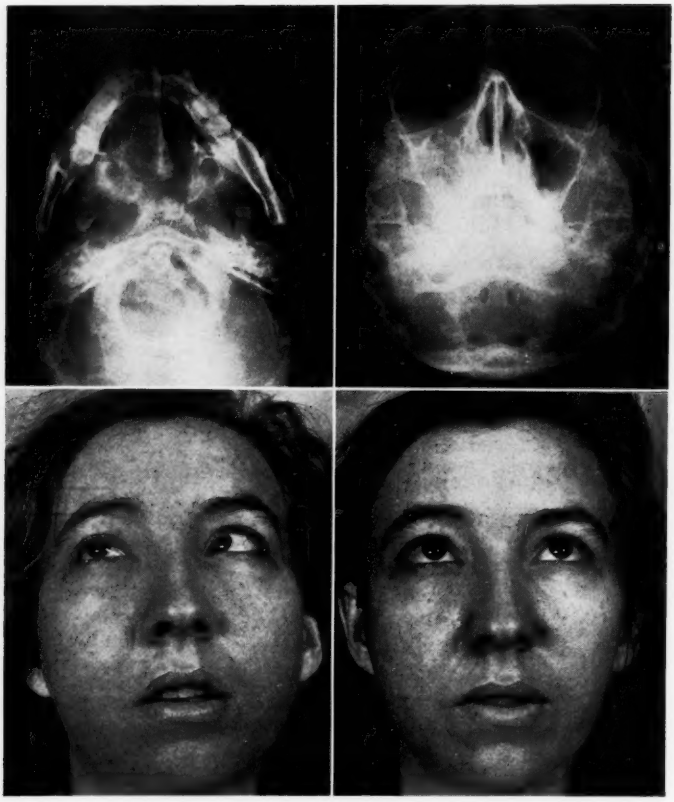


Fig. 4.—Roentgenograms made before treatment and photographs made before and after treatment in Case 2. The paralysis of the external rectus of the right eye produced by upward extension of a transitional cell carcinoma of the pharynx through the foramen lacerum disappeared after x-ray therapy and she has remained well for two years.

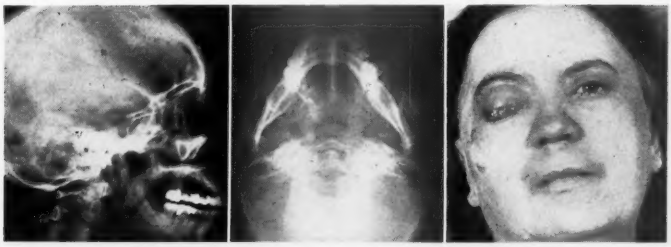


Fig. 5.—Roentgenograms of the skull and a photograph of Case 3 made before treatment. A squamous cell carcinoma, grade I, of the nasopharynx has destroyed both sphenoids and the lower portions of the posterior horns of the sella turcica and has entered the right orbit producing an exophthalmus.

He discovered a tumor in the nasopharynx and removed a specimen which was diagnosed as sphenoccipital chordoma, moderately anaplastic.

At admission a greyish tumor mass filling the upper nasopharynx was described. No cervical nodes were palpable and no evidence of tumor extension could be detected.

Portals measuring 10 x 10 cm. were laid out over the sides of the face and centered over the nasopharynx. Daily doses of 315 roentgens were administered alternately to the two portals until each had received a total of 3150 roentgens using the factors described in Case 1.

On May 2, 1942, the deafness, the tinnitis and the discharge had disappeared but she complained of some dizziness and a "cracking noise" in the back of the head when she turned it from side to side. The tumor was replaced by a slightly elevated mass in the posterior nasopharynx resembling granulation tissue. On May 13, 1942, she felt well but the mucosa at the original site of the tumor had a somewhat greyish appearance.

She has remained well for one year but occasionally has symptoms suggesting a temporary obstruction of the left eustachian tube. The results obtained in this case indicate that all chordomas are not radioresistant.

CONCLUSIONS

1. About 85 per cent of the malignant tumors encountered in the nasopharynx are radiosensitive and the outlook in the earlier cases is no longer gloomy.

2. Better results will be obtained when physicians learn to make an early diagnosis and institute proper irradiation therapy before dissemination has occurred.

3501 GASTON AVENUE.

REFERENCES

1. Furstenberg, A. C.: Malignant Tumors of the Nasopharynx, Surg. Gyn. & Obst. 66:400-404, 1938.

2. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, Arch. Neurol. & Psychiat. 8:412, 1923.

3. New, G. B.: Highly Malignant Tumors of the Nasopharynx and Pharynx, Trans. Am. Acad. Ophth. 36:39-44, 1931.

4. Jackson, C.: Primary Carcinoma of the Nasopharynx, J. A. M. A. 37:371, 1901.

5. Needles, W.: Malignant Tumors of the Nasopharynx, J. Nerv. & Ment. Dis. 86:373-398, 1937.

6. Martin, H. E. and Stewart, F. W.: Spindle Cell Epidermoid Carcinoma, Am. J. Cancer 24:273, 1935.

7. Quick, D., and Cutler, M.: Transitional Cell Epidermoid Carcinoma, Surg. Gynec. & Obst. 45:320, 1927.

8. Schmincke, A.: Ueber lymphoepitheliole Geschwülste, Beitr. z. path. anat. u.z. allg. Path. 58:161, 1921.

9. Martin, H. E., and Blady, J. V.: Cancer of the Nasopharynx, Arch. Otolaryng. 32:692, 1940.

10. Reverchon. Deux cas de tumeur du rhinopharynx, Bull. d'otorhinolaryngol. 20:245, 1922.

11. Collet and Rebattu. Etude sur la propagation intracranieme des tumeurs du pharynx, Arch. internat. de laryngol. 29:945, 1923.

12. Gaillard, R. A.: A propos des tumeurs du pharynx à point de depart peritubaire, Annd. d. mal. d. l'oreille, du larynx 42:772, 1923.

13. Martin, Chas. L.: Complications Produced by Malignant Tumors of the Nasopharynx, Am. J. Roentgenol. 41:377, 1939.

14. Barre, J. A., and Stoeber, R.: Tumeur due carrefour petro-sphenoidal d'origine nasale, Rev. d'oto-neuro-ocul. 2:81, 1924.

15. Bach, A. C., Lederer, F. L., and Palevsky, S. N.: Nasopharyngeal Carcinoma, Arch. Otolaryng. 31:529, 1940.

16. Lenz, M.: Roentgen Therapy of Primary Cancer of the Nasopharynx, Am. J. Roentgenol. 48:816, 1942.

17. Salinger, S., and Pearlman, S. J.: Malignant Tumors of the Epipharynx, Arch. Otolaryng. 23:149, 1936.

18. Coutard, H.: Roentgen Therapy of Epitheliomas of the Tonsillar Region, Hypopharynx and Larynx from 1920 to 1926, Am. J. Roentgenol. & Rad. Ther. 28:313, 1932.

19. Martin, Chas. L.: Carcinoma of the Upper Pharynx, Am. J. Surg. 30:36, 1935.

20. Martin, Chas. L.: Malignant Tumors of the Throat, Surgery 2:381, 1937.

XIII

SPECIFIC IN VITRO ACTION OF SULFONAMIDE COMPOUNDS ON PATHOGENIC ORGANISMS*†

MILAN NOVAK, M.D.

CHICAGO

Since the dawn of medical science, there has existed a desire to control disease with chemical substances which could be administered orally or parenterally. The discovery of the bacterial etiology of disease by Koch and Pasteur during the latter part of the last century gave an added stimulus to research in the field of specific therapy. In 1890 the first success was obtained by Von Behring and Kitasato in the specific treatment of diphtheria with antitoxin. The hope for the cure of all bacterial diseases by serum therapy was dispelled when investigators found that antitoxins are effective only against bacteria which produce exotoxins, and it was soon realized that relatively few bacteria form these toxins.

A new hope for specific therapy for communicable diseases followed the discovery of arsphenamine for the treatment of syphilis by Ehrlich in 1907. It is of some interest to realize that Ehrlich's discovery was made just one year after Wassermann described his complement fixation test and only two years after Treponema pallidum had been proved to be the causative organism in the disease. Ehrlich, believing his discovery would lead to the salvation of the human species by means of chemotherapy of all infectious diseases, named his substance "salvarsan." His hope, however, was not realized during his lifetime, although a substance which was to later rank as one of the world's most important compounds was synthesized in 1908 a few years before he died. The compound now known as sulfanilamide had no importance for a quarter of a century, until the epoch making discovery of Domagk in 1935. He showed the efficacy of sulfamido-chrysoidin in chemotherapy of bacterial infections, which fact led directly to the realization by American and British workers that Domagk's dye was actually hydrolyzed in the body to sulfa-

*From the Department of Bacteriology and Public Health, Chicago Colleges, University of Illinois.

†Presented before the Chicago Laryngological and Otological Society, Nov. 2, 1942.

nilamide and that this latter compound was the active substance. Sulfanilamide is today considered as the greatest discovery in specific therapy of bacterial infections since antitoxins came into general therapeutic use.

Several thousand compounds have been synthesized since these initial investigations and several of them have been accepted for general use in rather rapid succession. The resulting confusion which exists in the minds of many is not surprising for it is sometimes difficult to decide which drug to choose for a given condition.

Several considerations regarding the character of the drug must be made before a logical choice can be decided upon. Specificity, toxicity, solubility (including absorption and excretion) and cost are among these factors. One must also decide whether it is more desirable to have a primarily local effect by local application or a general effect by systemic distribution of the drug following oral or parenteral administration.

The bacteriologists are interested primarily in the specificity of the several drugs for various species of bacteria. We have come to accept the view that the sulfonamide compounds have a deleterious effect on bacteria by interfering with their enzyme systems. Bacteria become confused because of the structural similarity between the sulfonamides and para-amino benzoic acid—the latter being an accessory growth substance required for bacterial reproduction. When a bacterium mistakes a sulfonamide molecule for one of the growth accessory substances, it ceases to reproduce and, since the primary object of life in bacterial species is to multiply their numbers (since they usually find themselves in an abundance of food and a warm environment and hence need not direct their efforts to secure food or shelter), they soon lose interest in life and die when reproduction is interrupted.

In considering specificity in the action of the sulfonamides, one must emphasize that specific action is demonstrated only in low concentrations of the drugs such as those found in the ordinary therapeutic blood levels. In higher concentrations, such as those found in wounds following local application of the powdered drugs, there is complete inhibition of bacterial multiplication regardless of the drug used or the species of bacteria present. In local wound therapy, therefore, factors other than specificity should be considered in the choice of a drug. The low cost of sulfanilamide has made it a drug of choice in local wound therapy. However, there are occasions when a less soluble compound is preferable. Sulfanilamide applied locally

to wounds is absorbed in about 24 hours so that daily replacement is necessary. Sulfathiazole and sulfadiazine, being much less soluble, are preferable for local administration when the wound is such that daily applications of a drug are inconvenient or undesirable. The important point is that any of the common sulfonamides used locally will completely inhibit all bacteria in the concentrations present when applied to wounds, and therefore specificity need not be reckoned with in such situations.

In the general systemic infections, where it is desirable to maintain inhibitory concentrations of the drugs in all the tissues, one must consider specific action on various bacterial species. In spite of the rapid sequence in the introduction of new sulfonamide compounds, sulfanilamide still is considered the drug of choice in infections caused by the beta hemolytic streptococcus. It is a curious fact, however, that the anaerobic strains in this group of organisms are not susceptible to any of the sulfonamide derivatives. The effect on alpha hemolytic streptococci (viridans type) is definitely inhibitory in vitro, but the drug has little therapeutic significance in such diseases as endocarditis which are caused by this group of organisms. Sulfanilamide has been found useful in the treatment of trachoma and lymphogranuloma venereum, diseases supposedly caused by a virus—a fact of especial interest since virus diseases are not usually amendable with the sulfonamides. Brucella infections have likewise been cleared up by use of sulfanilamide.

Sulfapyridine, formerly popular, has fallen into disuse because of its numerous toxic actions. It is popular in the treatment of influenzal meningitis but recent experiments in our laboratory have shown that sulfathiazole or sulfadiazine are equally effective in the test tube against several strains of Hemophilus influenzae while sulfanilamide is relatively ineffective.

Sulfathiazole has a specific action on pneumococci, gonococci, meningococci, staphylococci and influenza bacilli in test tube experiments. However, the drug is not effective in meningococcal or influenzal meningitis because it does not penetrate into the spinal fluid in sufficient concentration. This is an illustration of the inability to transpose test tube results on specificity to practical applications in actual infection.

Sulfadiazine has the widest range of activity as far as bacterial species are concerned. It is effective against all of the organisms inhibited by sulfanilamide and sulfathiazole together with a few

additional ones such as Escherichia coli. It has found a wide use for both local and general therapy because of its several advantages.

The most recent addition to this group of drugs, sulfaguanidine, is one which has a specific local action on normal intestinal flora. It has been found of value in decreasing the number of bacteria within the intestinal tract. Succinyl sulfathiazole has a similar local action specific against Escherichia coli and intestinal anaerobes as well as on dysentery organisms. Both drugs are useful preoperatively in gastrointestinal surgery to minimize massive contamination of the peritoneum during the operation.

CONCLUSIONS

1. In sufficiently high concentrations, such as are present in local treatment, all of the common sulfonamide derivatives are bacteriostatic to all species of bacteria.

2. Specificity of drug action against a given bacterium is demonstrated only in lower concentrations such as those obtained in systemic treatment.

3. The choice of a sulfonamide drug for systemic treatment should be based primarily on specificity; for local treatment, the accessibility of the wound and the solubility of the drug should receive the most consideration.

4. Specificity of action as demonstrated in the test tube cannot be used as a sole criterion for the selection of a sulfonamide derivative for a given condition, since toxicity, cost and relative solubility are equally important to consider.

CHICAGO COLLEGES
UNIVERSITY OF ILLINOIS
1853 W. POLK STREET.

XIV

PHARMACOLOGIC DEVELOPMENT OF THE SULFONAMIDES*

FRANK T. MAHER, PH.D.

CHICAGO

Sulfonamide chemotherapy grew out of a routine investigation of antiseptic agents by Domagk[1] and his associates in 1925-1933. Their first clinical use was reported by Foerster.[2] Following Foerster's report, we saw a period of about five years of rather indiscriminate use, during which therapy suffered from a distinct lack of sound experimental background.

During this period, no reliable method was available for the estimation of the sulfonamide content in biologic samples, and valuable data concerning bacterial metabolism and basic pharmacology were not yet available. As a result, investigations suffered from errors of which we are at least aware today. Early bacteriostasis studies drew erroneous conclusions, while acute toxicity studies were crude and unsound.

It is true that much valuable work was done during this period. Yet, many of the studies ended in speculation rather than solid conclusion, and the high incidence of toxicity is not surprising in view of the inadequate nature of the experimental development. Sulfonamide chemotherapy showed a reversal of rational procedure—here the results of therapy were so revolutionary that the clinical picture tended to run away from the slower progress of fundamental study.

Rational progress really began with the development of methods of quantitative analysis by Fuller[3] and by Marshall[4] in 1937. During the past five years, we have seen the increasing importance of basic study to sulfonamide chemotherapy. The past five years have standardized controlled studies in basic properties and in the extensive synthesis of new derivatives. Closer studies have been made into bacterial metabolism in relation to the drug and to the disease, and clinical as well as experimental attempts to correlate these findings with fac-

*Presented before the Chicago Laryngological and Otological Society, Nov. 2, 1942.

tors of resistance have been made. All these studies have been directed toward better treatment.

Chemists have given us four or five thousand derivatives of sulfanilamide, most of which have received careful routine study. Of these, only seven or eight have achieved recognition in American therapeutics. Our principal purpose is to point out briefly the importance of the studies in basic fields and in the selection and development of these better chemotherapeutic agents.

For convenience, we may divide the commonly used sulfonamides into three general groups:

1. Azo derivatives of the azosulfamide or neoprontosil type. These we believe to be effective by their splitting in the body to yield free sulfanilamide. Subsequent pharmacology is primarily that of sulfanilamide.

2. Compounds differing from sulfanilamide only by groupings around the S atom. This group includes sulfapyridine, sulfathiazole, sulfadiazine and sulfapyrazine. Along with changes in structure, these compounds offer correlated variations in pharmacologic properties, in clinical effectiveness, and in toxic properties.

3. Compounds possessing more specific pharmacologic properties. These have particular applications in therapy. This group includes sulfaguanidine and succinyl sulfathiazole (sulfasuxidine).

Following is a brief consideration of some general types of pharmacologic investigation and the importance such studies have had upon the clinical progress of the sulfonamides.

Studies in experimental sulfonamide therapy. These studies are of course fundamental to the treatment of clinical infection. They, together with bacteriologic investigations in vitro and in vivo and extended by clinical investigations, have furnished data concerning the following:

1. Comparative antibacterial activity, with classification of susceptible and nonsusceptible strains. Variations with different animal species have pointed to caution in interpreting results, and both in vitro and in vivo studies are necessary.

2. The relation of species. Specific variations in properties in relation to chemical structure remains an empirical problem. We can

observe interesting and important correlations between activity and structure, but we do not understand the fundamental relations.

3. Comparative toxicity.

Absorption studies. The clinical use of sulfaguanidine followed Marshall's[4] observation that this drug is very poorly absorbed from the gut. In similar fashion, succinyl sulfathiazole was introduced for treatment by Poth and Knotts[5] because of its indifferent absorption. It should be noted that these drugs exhibit, in general, antibacterial properties and toxic potentialities typical of the sulfonamides. Their specialization in intestinal infection is due primarily to their retention in the gut.

We may just point out the slow, irregular absorption of sulfapyridine and the rapid absorption of sulfathiazole. Another point concerning absorption is that sulfanilamide is well absorbed from the rectum, while sulfadiazine apparently is not. Thus the rectal route is open for sulfanilamide, but not for sulfadiazine.

Distribution studies. In general, the sulfonamides are uniformly and rapidly distributed after absorption, with little variation in affinity for particular organs or tissues. In contrast to this, we have seen that sulfathiazole does not readily pass into the spinal fluid. This pharmacologic difficulty militates against the use of sulfathiazole in meningeal infections. Sulfanilamide and sulfadiazine offer advantages here because of their ability to gain access to the spinal fluid.

Detoxification studies. All sulfonamides are detoxified to a varying extent by acetylation in the liver and the reticulo-endothelial system. The acetyl derivative so formed is therapeutically inert, and conjugation therefore represents a net loss of active drug. This loss was particularly significant in the case of sulfapyridine, due to the high level to which this drug is acetylated in the body. Sulfathiazole, sulfadiazine and sulfapyrazine have the advantage of a small loss by such conjugation.

Excretion studies. The excretion of free and conjugated sulfonamides occurs primarily through the urine. The irregular elimination of sulfapyridine and the rapid elimination of sulfathiazole offer significant variations for study.

Sulfonamides are also excreted into the stomach, attaining relatively high concentrations in the gastric juices. This phenomenon is a factor in the nausea and vomiting associated with sulfonamide

therapy, and is also a problem in attempts to obviate these reactions by parenteral administration or the use of enteric-coated forms.

These fundamental studies gain an added importance when we consider a brief summary of them:

All the factors mentioned bear upon the concentration of free sulfonamide in the appropriate body fluid. This adequate concentration is so important that it forms the present basis for adequate dosage, for uniform maintenance of adequate drug levels is considered essential to optimal therapy, and control by chemical estimation is now routine. Such adequate blood or fluid levels are favored by optimal balance and uniformity in rates of absorption, distribution, detoxification and excretion.

Sulfanilamide, sulfadiazine and sulfapyrazine are absorbed and excreted at rates favoring adequate blood levels. Sulfadiazine and sulfapyrazine have the additional advantage of being conjugated to the lowest level in the sulfonamide group.

In the case of sulfapyridine, slow, irregular absorption and excretion, coupled with extensive conjugation, render blood levels more difficult of maintenance. The high level of conjugation also favors the formation of urinary calculi.

Sulfathiazole is rapidly absorbed and excreted, hence again it may be difficult to maintain desired blood levels in treatment. These same factors, coupled with the low conjugation of sulfathiazole, are of advantage in urinary infections, since they lead to the rapid development of high concentrations of free drug in the urine.

The formation of calculi in the urinary tract is favored by the relatively poor solubility of the acetylated derivatives. Urolithiasis is particularly prevalent with sulfapyridine because of extensive conjugation, and with sulfathiazole because of rapid excretion. Sulfadiazine and sulfapyrazine offer the seeming advantages of lower conjugation and more soluble acetyl derivatives, yet recent reports indicate a significant occurrence of urolithiasis with sulfadiazine.

Physical factors are also of importance in the local use of sulfonamides. In such use, the free form of the sulfonamide attains a high concentration in tissue fluids for extended periods of time. We are thus making use of agents which are relatively weak antibacterial agents, but which may exert their effects over extended periods with little damage to the tissues of the host. In such use, sulfanilamide

and sulfadiazine offer the advantages of slow absorption and a minimal tendency to clump and set up foreign-body reactions in local sites. Sulfathiazole, in contrast, exhibits a more marked clumping tendency, and its more rapid rate of absorption correspondingly reduces the period of effective local concentration.

Toxicity studies. We are now well aware that studies in acute toxicity in animals do not furnish a true picture of clinical danger in sulfonamide therapy. The most serious objections to the use of sulfanilamide lie in the possibility of damage to the erythrocytes, the granulocytes and the liver. With the development of sulfanilamide derivatives, these dangers are in general significantly reduced, yet with these, it is interesting to note that some particular type of untoward reaction may become prominent. These may be summarized briefly as follows:

Sulfapyridine: Nausea, vomiting, urolithiasis.

Sulfathiazole: Drug fever, dermatitis, nausea, urolithiasis.

Sulfadiazine: Recent reports indicate that urolithiasis may follow sulfadiazine therapy, and Hellwig and Reed[6] have reported evidence of primary tubular degeneration effected by sulfadiazine.

It should be noted here that while para-aminobenzoic acid combats the antibacterial activity of the sulfonamides, it does not prevent or attenuate toxic reactions following their use.

SUMMARY OF THE PRINCIPAL LINES OF STUDY

1. Studies into bacterial metabolism, with modifications occurring in disease and under drug action.

2. Studies into the chemical and pharmacologic behavior of drugs in healthy and in diseased animal bodies.

3. Studies into the physiology of the host and the relation of its vital functions to drug action and to the development of disease processes.

Such studies are pointed toward a clarification of the processes by which sulfonamides accomplish their effects and toward the development of derivatives possessing wider therapeutic application with a lessened incidence of toxicity. We do not as yet have the perfect derivative and many pieces in the puzzle are lacking; yet, the past five years have seen tremendous developments in that direction. We have attempted to point out briefly the importance and significance

which fundamental control studies have had, and will continue to have, in that developmental picture.

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF ILLINOIS.

REFERENCES

1. Domagk, G.: Ein Beitrag zur Chemotherapie der Bakteriellen Infektionem, Deutsches Med. Wchnschr. 61:250, 1935.

2. Foerster: Sepsis im Anschluss an ausgedehnte Periporitis, Heilung durch Streptozon, Zentralbl. f. Haut. u. Geschlectskr. 45:549, 1933.

3. Fuller, A. T.: Is p-Aminobenzenesulfonamide the Active Agent in Prontosil Therapy?, Lancet 1:194, 1937.

4. Marshall, E. K., Jr., Emerson, K., and Cutting, W. C.: Para-Aminobenzenesulfonamide: Absorption and Excretion—Method of Determination in Blood and Urine, J. A. M. A. 108:953, 1937.

5. Poth, E. J., and Knotts, F. L.: Succinyl Sulfathiazole, New Bacteriostatic Agent Locally Active in the Gastro-Intestinal Tract, Proc. Soc. Exper. Biol. and Med. 48:129, 1941.

6. Hellwig, C. A., and Reed, H. L.: Fatal Anuria Following Sulfadiazine, J. A. M. A. 119:561, 1942.

XV

CLINICAL EXPERIENCE WITH SULFONAMIDES IN OTOLARYNGOLOGY*

GEORGE S. LIVINGSTON, M.D.

CHICAGO

Sulfonamide therapy in otolaryngology finds its chief value when used in the acute infections of this field. A consideration of its effectiveness is important, but is sometimes difficult to appraise. Since most acute infections of the ear, nose, and throat are self-limited, tending toward spontaneous resolution, any therapeutic measures are likely to appear valuable but may be only incidental to the natural course of the disease. When we consider, however, the proved effectiveness of sulfonamides in such highly fatal diseases as otitic meningitis, a solid therapeutic basis has been established which warrants a consideration of their use in less severe infections.

Statistics do not lend themselves well to the appraisal of the results of treatment of simple, self-limited infections. Close observation of individual cases is more helpful to the clinician in forming an opinion. In acute otitis media, for example, the course without sulfonamides is unpredictable. Cases vary from the mildest to the most severe. If sulfonamides are given early and adequately, there is usually a rapid, even a critical response, with complete recovery in a few days. In the writer's experience and that of many pediatric colleagues, the number of cases requiring myringotomy has been markedly lessened. The proportion of cases that fail to respond is relatively small. There are several possible causes for such failures, namely, late administration, wrong choice of drug for the particular organism causing the infection, inadequate dosage, irregular administration, and an exceptionally virulent infection with poor immunity response by the patient. These virulent infections will probably continue to cause complications in spite of adequate treatment.

At Children's Memorial Hospital in 1941 and 1942, all patients with acute mastoiditis were treated preoperatively with sulfonamides. This is proof enough that the drugs will not cure all cases of otitis

*Presented before the Chicago Laryngological and Otological Society, Nov. 2, 1942.

media. Nevertheless, a marked decrease in the number of complications has been observed. While it has not been possible to correlate accurately the number of cases of otitis media with the number of cases of mastoiditis, a review of our statistics reveals a significant trend. The number of cases of mastoiditis has always varied markedly from year to year. From 1932 to 1938 inclusive the annual number of cases varied between 52 and 112. In 1939 there were 87 cases, 13 of which had sulfonamide treatment. In 1940 there were 114 cases, of which 34 were so treated. In 1941 there were 49 cases, all of which had sulfonamides, and in 1942 all the patients received the drugs, but only 17 have been operated on to the present time. This unprecedentedly low figure, we believe, reflects the increasingly widespread and more efficient use of sulfonamides by pediatricians and general practitioners early in the course of acute upper respiratory and otitic infections. From 1940 until the present time there have been 180 cases of acute mastoiditis. In this group there were 5 cases of meningitis with one death, and one case of sinus thrombosis, which recovered.

At present, sulfadiazine is the drug of choice, because it is effective against a greater variety of organisms, is less toxic, and is less likely to cause renal and other complications than the other sulfonamides. The dosage of one grain per pound of body weight in 24 hours is usually sufficient to maintain an adequate blood level. It is given in divided doses at four- or six-hour intervals. If the infection is unusually severe, more heroic treatment is indicated. Especially when sepsis or meningitis are present, it is imperative to establish a high blood level promptly. This can be done by giving the 24 hour requirement as a first dose, or by intravenous infusion of a five per cent solution of sodium sulfadiazine in distilled water. In such cases blood levels of 10 mg. per 100 cc. should be maintained until clinical improvement and negative blood and spinal fluid cultures show that the infection is definitely under control. Then the dosage may be gradually reduced. During the course of treatment a close watch must be kept on the blood count, the urinary output, and the microscopic urinalysis. It is probably better to give sulfadiazine orally after, rather than before, meals whenever possible. Peterson and Finland[10] have determined that it is absorbed more slowly but more completely when given after a meal than on a fasting stomach. Added alkali, such as an equal amount of sodium bicarbonate, increases the amount of drug absorbed when given after a meal. Sodium bicarbonate hastens absorption when given on an empty stomach, but does not increase the amount absorbed.

Many reports have dealt with the possibility of developing a sulfonamide-fast organism if the early dosage is too low, and others with the danger of relapses if the drug is withdrawn before recovery is complete. Although sulfonamides have proved their value, they should not be relied upon solely in the treatment of infections. The usual indications for other measures must be heeded as they arise and applied as needed.

Toxic reactions to sulfonamides are quite common, although fortunately the severe ones are not. Nevertheless, Lyons and Balberor[7] found that one-third of all their patients treated with sulfonamides a second time developed a sensitivity sufficient to interfere with further use. The most frequent evidences of toxicity are nausea and vomiting, often accompanied by headache and malaise. If mild, they may subside even though treatment is continued. If severe, however, the drug may have to be withdrawn. These reactions usually occur early in the course of treatment, and are most frequently encountered when sulfapyridine or sulfathiazole are used. Sensitization, if it occurs, usually becomes manifest between 9 and 12 days after the first administration of the drug. This so-called sulfonamide shock is characterized by a chill or by chilliness, followed by a sharp rise in temperature to 104 F. or higher, and is frequently accompanied by an itching cutaneous eruption. With sulfathiazole, conjunctival injection is also often observed. The appearance of this syndrome is a warning to stop the drug, as its continuance may lead to more serious complications. If this is done promptly the symptoms subside in two to four days. Subsequent administration is quite likely to cause a repetition of the reaction, even though a different sulfonamide is used.

Nelson[9] reported the case of a woman with cystitis and urethritis who was treated with sulfathiazole without initial reaction. On the eighth day 5 grams caused a toxic reaction, which stopped when the drug was withdrawn. On the twenty-second day 4 grams of sulfathiazole caused a similar reaction. On the thirtieth day, 2 grams of sulfathiazole, giving a blood concentration of 3.1 mg. per 100 cc., caused a reaction. On the thirty-eighth day, 4 grams of sulfadiazine, producing a blood level of 3.3 mg. per 100 cc., caused another reaction. On the fiftieth day, 4 grams of sulfapyridine, with a blood level of 5.1 mg. per 100 cc., caused a reaction, and on the sixty-fourth day, after 10 grams of sulfanilamide, with a blood concentration of 6.6 mg. per 100 cc., there was another reaction. Gallagher[3] has observed sensitivity to persist for two years in one patient.

Apparently the mechanism is one of true sensitization. Although Wedum[13] could not demonstrate it in animals with simple uncombined sulfonamide compounds, he was able to do so by the use of azoproteins. His experiments using sulfonamides combined with egg white, human serum and beef serum produced sensitization, as demonstrated by skin tests, anaphylaxis, and precipitation tests. While the strongest reactions occurred with the specific sensitizing sulfonamide azoprotein, weaker crossed reactions also occurred when other members of the sulfonamide group were used.

Although the proportion of complications is not large considering the widespread use of these drugs, the literature contains many reports of agranulocytosis, acute hemolytic anemia, hepatitis, hematuria, and anuria. Sulfathiazole and sulfapyridine have been known for some time to be likely to cause uroliths because of their high rate of acetylation. Sulfadiazine, with a low degree of acetylation, may, however, also cause severe renal damage. Lederer and Rosenblatt[5] reported four cases of death attributable to sulfathiazole in which there was widespread visceral focal necrosis. Merkel and Crawford[8] also reported four such deaths. In these cases the fluid intake and urine output were adequate, and the highest blood level was 10 mg. per 100 cc. There were found many discrete areas of focal necrosis in the lungs, the kidneys, the liver, the spleen, and the bone marrow. Sulfadiazine also is not entirely without guilt in this respect. Raines[11] reported two cases of ureteral obstruction following its use. Bradford and Shaffer[1] had a case of fatal urinary suppression from sulfadiazine, in which the autopsy showed acetylated crystals in the renal pelves and tubules, with adjacent ulceration, intense inflammation, and necrosis. In the case reported by Hellwig and Reed,[4] the patient had taken 24 grams of sulfadiazine in nine days. Fatal anuria resulted. At autopsy, the kidneys showed a severe degeneration of the convoluted tubules, similar to that found in mercury poisoning. These references are cited not to deter one from the properly indicated use of these valuable drugs, but to sound a note of caution against their promiscuous and needless administration.

Many problems may arise during a course of sulfonamide treatment, some of which are difficult to solve. One of these is the well-known masking effect in a case of acute otitis media. Many cases have been reported, and every otologist has had experience with them. If all symptoms have subsided except otorrhea, and this persists beyond the second week, one should become suspicious of masking. From this time on, even slight symptoms must be carefully watched for. A slight rise in temperature or in the leukocyte count, an in-

crease in the discharge, transient headache or ear pain, which without sulfonamides would cause no great concern unless they persisted or increased in severity, may now indicate a well-advanced complication. Persistence of medication may still result in a cure, or it may lead to disaster. It is safest at this point to stop the sulfonamide. If an exacerbation occurs, the surgical indication will then be obvious.

An even more difficult problem sometimes arises in differentiating between a drug reaction and an otitic complication. If, during the course of treatment, the patient has a chill and a sharp rise in temperature, it is difficult to decide between sulfonamide shock and otitic sepsis, unless a cutaneous eruption appears. The rash may appear a day or two later, or not at all. The leukocyte count is unreliable since sepsis may occur with leukopenia, and some sulfonamide reactions produce a hyperleukocytosis. A blood culture may be helpful, but one must be sure to add para-aminobenzoic acid to the culture medium in order to neutralize the bacteriostatic effect of the sulfonamide in the blood. The drug must be stopped to determine the true status of the patient. Many sulfonamide reactions cause fever, headache, nausea, and vomiting. Such a picture requires a study of the spinal fluid to rule out meningitis. If an intracranial complication proves to be present, the situation is clarified as to the indication for surgery, but unfortunately the patient must be deprived of the sulfonamide, at least temporarily, at the time when he needs it most urgently. A difficult situation arises when a severe otitic infection seems to be yielding well to sulfonamides, though recovery is not yet complete, and a toxic reaction occurs serious enough to preclude further medication. At this point, an exacerbation of the infection with possible complications is likely to occur.

The writer's experiences with oral sulfonamide therapy in acute infections of the nasal sinuses run generally parallel to those in acute otitic infections. In conjunction with other indicated measures, sulfonamides usually effect quicker relief, a shorter course, and less tendency to complications than when not used. In acute throat infections also, sulfonamides seem to hasten recovery. In patients with beginning peritonsillar invasion, before suppuration has occurred, prompt administration of sulfonamides has produced resolution in many instances where an abscess formation would otherwise be anticipated.

The local use of sulfonamides has now become well established and is in certain instances more satisfactory than systemic adminis-

tration. When placed directly at the site of infection, a much higher and therefore more effective concentration of the drug can be established where it is most needed than can be accomplished by oral administration. This not only insures more complete bacteriostasis but avoids toxicity, since very little absorption into the blood stream occurs. The compounds are not irritating to the tissues if the amount implanted is not excessive.

The writer[6] has previously reported on the use of sulfanilamide and sulfathiazole in the mastoid cavity after operation. In 1941, in 28 consecutive simple mastoidectomies, sulfanilamide crystals were implanted in the cavity, followed by closure with a rubber tube drain. The postoperative course in these cases paralleled those previously operated on without the use of sulfanilamide. The period of care until complete healing was accomplished varied between three and six weeks. In the next 13 cases, sulfanilamide was implanted in 8, and sulfathiazole in 5, and the wounds were sutured without drainage. In 11 cases there was healing by primary union and a dry middle ear in an average of 6.4 days. The shortest time was 4 days, and the longest was 9. The appearance of the wound in all these cases was remarkable for the absence of soft-tissue inflammatory reaction. In the cases with subperiosteal abscess there was rapid progressive diminution of swelling, which usually had disappeared completely in 3 or 4 days. The 2 unsuccessful cases drained 30 and 31 days respectively. In the light of subsequent experience it appears that these failures were due to an excessive amount of the drug in the wound. This causes a great quantity of serous exudation, which in these cases was sufficient to rupture the wound. In one case, with 4 grams of sulfanilamide in the cavity, there was found 24 hours later a blood level of 4.7 mg. per 100 cc., on the second day 0.95 mg., and on the third day none. Even with this needlessly large dose, the greatest concentration of the drug was less than is usually maintained by oral administration and is present for only a day or two. A total of 38 patients have now been operated on by this method with only one additional failure to heal by primary union.

A number of patients with chronic suppuration of the middle ear and a large tympanic perforation were treated by insufflation of sulfathiazole powder. The fetor and purulency of the discharge diminished, but the quantity usually increased, and large masses of caked powder accumulated which were difficult to remove. In the cases of cholesteatoma, the drug in no way altered the pathologic picture. The benign cases with central perforation and no bone necrosis yielded more satisfactorily to iodine-boric powder.

In the treatment of acute empyema of the maxillary sinus local sulfonamide treatment has proved to be remarkably effective. An aqueous suspension of sulfathiazole or sulfadiazine, injected into the antrum after lavage, has stopped the suppuration in one to three treatments in 22 cases. The same method was used in 14 cases of chronic antrum empyema. In these, improvement was noted in all, as evidenced by a marked decrease in the amount and odor of the discharge. In 9 cases, suppuration ceased after six to eleven semiweekly instillations, but recurred with the next cold. In the remaining 5 cases, although improvement was manifest, suppuration did not cease. A Caldwell-Luc operation was required. Here again, sulfathiazole proved valuable. In the postoperative period the powder was insufflated into the sinus two or three times a week. The cases were notable for the absence of soft tissue reaction and the rapid cessation of suppuration. Similarly gratifying results were obtained in the postoperative care of four cases of intranasal ethmosphenoidectomy, using the same method. These experiences lead to the conclusion that local sulfonamide treatment is of considerable value in chronic sinus suppuration, but will not alone effect a cure if the pathology is such that it requires surgical eradication.

The recent introduction of microcrystals of sulfathiazole has eliminated certain difficulties in local therapy. They are prepared, as reported by Chambers and his co-workers,[2] by crystallization from a solution of sodium sulfathiazole at a low temperature, applying violent agitation by means of sonic vibration. They can be easily suspended in water up to 30 per cent by weight. Clumping does not occur, and the minute size of the crystals favors more rapid solution. In this form no foreign-body reaction occurs. None of the drug could be found in the tissues ten days after implantation. Silcox and Schenck[12] reported on the local application of a suspension of microcrystalline sulfanilamide and sulfathiazole in various otolaryngologic diseases. They noted the ease of introduction, the absence of clumping and of irritation, and the negligible absorption into the blood stream. They found a 5 per cent suspension to be adequate for all purposes and obtained excellent results, especially in the treatment of acute and chronic sinusitis. They found that its stability and hydrogen ion concentration were physiologically compatible with the membranes of the upper respiratory tract, and that there was apparently no inhibition of normal ciliary activity. Its chief advantage, in the writer's limited experience, is the ease with which it can be used in displacement filling of the posterior sinuses, as well as by cannula into the antrum.

The principles underlying the use of sulfonamides in otolaryngology must be formulated with regard to practice as we find it at the present time. Their widespread use in general practice and in pediatrics has apparently reduced the severity and duration of acute upper respiratory infections and the number of complications. The otolaryngologist is consulted chiefly for the unsuccessful cases. Here it is incumbent upon him to accurately appraise the clinical picture. The main problems he encounters are: inadequate administration or wrong choice of drug; an infection refractory to sulfonamides; differentiation between drug toxicity and an exacerbation of the infection; and the masking effect of sulfonamides. Where special technics are required, the otolaryngologist can supplement or supplant systemic sulfonamide treatment with its local application at the site of infection. This is especially advantageous whenever oral administration has been ineffective or when it must be discontinued due to toxicity. He further finds its local use to be a valuable adjunct in surgery, by eliminating an infection more quickly than can be accomplished by surgical methods alone.

185 North Wabash Avenue

REFERENCES

1. Bradford, H. A. and Shaffer, J. H.: Renal Changes in a Case of Sulfadiazine Anuria, J. A. M. A. 119:316 (May), 1942.

2. Chambers, L. A., Harris, T. N., Schumann, F., and Ferguson, L. K.: The Use of Microcrystals of Sulfathiazole in Surgery, J. A. M. A. 119:324 (May 23), 1942.

3. Gallagher, J. R.: Sulfanilamide Drug Fever; An Attack of Sudden Onset, New Eng. J. Med. 221:132 (July) 1939.

4. Hellwig, C. A. and Reed, H. L.: Fatal Anuria Following Sulfadiazine Therapy, J. A. M. A. 119:561 (June), 1942.

5. Lederer, M. and Rosenblatt, P.: Death during Sulfathiazole Therapy, J. A. M. A. 119:8 (May), 1942.

6. Livingston, G. S.: Local Sulfonamide Therapy in Acute Mastoiditis, J. A. M. A. 117:1081 (Sept.), 1941.

7. Lyons, R. H. and Balberor, H.: Development of Febrile Reactions during Second Course of Sulfathiazole; Preliminary Report, University Hosp. Bulletin, Ann Arbor, 7:19 (March), 1941.

8. Merkel, W. C. and Crawford, R. C.: Pathologic Lesions Produced by Sulfathiazole, J. A. M. A. 119:770 (July) 1942.

9. Nelson, J.: Acquired Sensitivity to Sulfonamide Drugs, J. A. M. A. 119:560 (June), 1942.

10. Peterson, O. L. and Finland, M.: The Effect of Food and Alkali on the Absorption and Excretion of Sulfonamide Drugs after Oral and Duodenal Administration, Amer. J. Med. Sc. 204:581 (Oct.), 1942.

11. Raines, S. L.: Ureteral Obstruction Following the Use of Sulfadiazine, J. A. M. A. 119:496 (June), 1942.

12. Silcox, L. E. and Schenck, H. P.: Use in Otolaryngology of Microcrystals of Drugs of the Sulfanilamide Group, Arch. Otolaryng. 36:171 (Aug.), 1942.

13. Wedum, A. G.: Immunological Specificity of Sulfonamide Azoproteins, J. of Infectious Dis. 70:171 (March), 1942.

OUR MEN NEED

★ BOOKS ★

SEND

ALL YOU CAN SPARE

MEDICAL OFFICERS in the armed services are on the alert for special journals. When you have finished with your copy of the ANNALS, leave it along with the other books you have enjoyed at the nearest collection center or public library for the 1943 VICTORY BOOK CAMPAIGN.

Clinical Notes

XVI

PETROSITIS AND MENINGITIS WITH RECOVERY*

MARVIN F. JONES, M.D.

NEW YORK CITY

A patient was referred to Dr. Thomas G. Tickle as a case of facial paralysis. Dr. Tickle asked me to see the patient because there was a paralysis of the external rectus muscle, rather severe pain over the distribution of the trigeminus nerve and a functionless facial nerve. A mastoid operation had been done some time previously and we knew that the surgeon who performed the operation was very capable.

When I first saw the boy, he looked sick. The patient walked into the clinic but bed was the place for him and to bed he was ordered. We learned that the weakness of the face and eye muscle was not present immediately following operation but came on gradually the next day. On March 16 (six days after operation), the facial nerve did not respond to stimulation by the faradic current. The patient was allowed to leave the hospital with all surgical aspects of the case except the facial paralysis progressing satisfactorily.

On March 23 (twelve days after operation), the patient complained of diplopia which began the day before. Diplopia was only present when he looked to the left. A paralysis of the left external rectus muscle was obviously the cause. At this point, an involvevent of the petrous process of the temporal bone was considered. Except for a 10,000 leukocyte count, all laboratory findings were negative. The offending bacteria were streptococcus hemolyticus and staphylococcus aureus.

This brings us to the day of admission to Manhattan Eye, Ear and Throat Hospital, March 23. The patient complained of little pain previous to admission but during that night he became restless and sedatives were administered to control a left side hemicrania. He was irrational, had a rising temperature and accompanying meningeal symptoms. Sulfadiazine had been ordered in 2.5 gram doses intravenously every six hours. Roentgenograms showed absorption

*Presented before the Eastern Section Meeting of the American Laryngological, Rhinological and Otological Society, Hartford, Conn., January 15, 1943.

of the cell walls in the petrous pyramid of the left side. The blood count now had some useful information. There was a leukocytosis of 25,800 with 92 per cent polymorphonuclear leukocytes. The spinal fluid was under pressure, cloudy, and on culture revealed a pneumococcus, type three. This finding was rather surprising since the pneumococcus three is not commonly so dramatic in its debut.

Further surgery seemed urgent and a petrous exploration was done. I found two channels leading into a cavity in the petrous part of the temporal bone. A small but gratifying amount of pus discharged through both channels. Since the patient had a meningitis, multiple incisions were made in the dura of the posterior and middle fossae. That night, as well as for many nights thereafter, this patient was considered hopeless. Sulfadiazine was administered with only one thought in mind, namely: to obtain the maximum concentration possible in the spinal fluid. We succeeded in maintaining the spinal fluid concentration near that of the blood. On some occasions the spinal fluid concentration exceeded the amount in the blood.

March 29 held a little more hope since there was no growth found in the spinal fluid. The daily spinal fluid was still under pressure and contained an average of 10 mg. of sulfadiazine. The blood picture had improved.

On March 30, the daily urine showed albumen but there was no growth from the spinal fluid. On April 1, the patient was given a supportive whole blood transfusion and soon became rational. Because blood and pus were present in the urine the sulfadiazine was discontinued. We were just beginning to breathe easier when again there was a sudden rise in temperature and a recurrence of a growth of pneumococcus type three in the spinal fluid. Pain and restlessness recurred and, since we had been led to believe the readministration of sulfa drugs was ineffective, our hopes again fell to zero. We started sulfadiazine again, giving 2.5 grams intravenously and supplementing these doses with doses by mouth whenever possible. Vomiting made the estimation of total dosage received inaccurate. Blood transfusions were ordered because constant nausea and vomiting were dehydrating the patient. Intravenous saline, to which was added vitamin B, was used to maintain body fluids and give nourishment.

On April 13, the patient had a retention of urine for 25 hours and the first sample obtainable again showed pus and blood. The sulfadiazine concentration at this time was 35 mg. in the spinal

fluid and 45 mg. in the blood. It was again stopped for five days. The sole nourishment was saline and vitamin B intravenously. There had been no growth of bacteria in the spinal fluid since April 9. The fever ceased on the 20th of April, albumen in the urine had greatly diminished,, the abducens nerve paralysis had cleared but the facial paralysis continued. The patient was discharged May 15. He is an 18-year-old male, an excellent looking specimen, so the army draft board is now annoying us.

COMMENTS

1. The concentration of sulfadiazine in the spinal fluid may be made to approximate that in the blood.

2. Sulfadiazine may be discontinued and again started with favorble results.

121 East 60th Street

XVII

PRIMARY THROMBOSIS OF THE COMMON CAROTID ARTERY WITH RECOVERY*

MARVIN F. JONES, M.D.

NEW YORK CITY

A case to be gratefully reported is one of a girl, aged five. It was reported to me that her trouble started with a sore throat, pain in the right ear and swelling of the cervical glands in the right side of the neck. On examination of the ear, a small draining sinus was found in the floor of the right auditory canal. The right tonsil was displaced toward the midline. The usual sulfa medication was said to have been started early. All seemed well and she was discharged from the hospital after eight days. A second admission to the hospital on the 28th of September was because of a recurring sore throat and increased cervical swelling. On the third day following her re-entry, the patient bled profusely from the mouth. A transfusion was given because of the exsanguination.

The patient was taken to the operating room where a searching procedure in the area of a posttonsillar ulcer produced severe venous bleeding and a state of shock. The bleeding was controlled by pressure. The blood count was reported as a leukocytosis of 50,600 and 85 per cent polymorphonuclears.

During the next few days the cervical swelling increased and there was a bulging of the inferior wall of the external auditory canal. Again the storm subsided and again increased in violence. A tumor of bluish color remained in the floor of the external canal. From this tumor, venous blood was aspirated.

An exploratory operation was performed and the report of the surgeon was as follows: An incision was made along the anterior border of the sternomastoid. The structures were defined. One enlarged cystic gland was removed. No abnormality was seen. The incision extended superiorly and posteriorly over the mastoid process. A dark, grayish mass was seen just behind the posterior belly of the digastric muscle, which appeared to be a thrombosed vein. The in-

*Presented before the Eastern Section Meeting of the American Laryngological, Rhinological and Otological Society, Hartford, Conn., January 15, 1943.

ternal jugular vein disappeared behind this mass. An attempt to dissect out this mass was made but it was inadvertently opened into. This exposed considerable thrombotic material and resulted in a great amount of venous bleeding. Bleeding was such that further dissection was impossible and it could be controlled only with pressure. The common carotid was tied with no demonstrable decrease in the amount of bleeding. The bleeding area was packed and the wound closed.

For days following the surgery, serious bleeding occurred from both the external neck wound and the throat. The supportive measures kept the blood picture surprisingly good. Her prothrombin time was low and vitamin K in large doses was given. Exacerbation of these same symptoms punctuated periods of comparative calm. January 13, 1941, brought her close to death following a hemorrhage from the ears, the mouth and the neck. She was then admitted on my service at the Manhatton Eye, Ear and Throat Hospital. I performed an exploratory operation immediately.

An incision was made paralleling the sternocleidomastoid muscle and extending from the mastoid tip to the suprasternal notch. The upper part of the neck was a hopeless mass of scarred and bleeding tissue. The carotid artery, the jugular vein and the vagus nerve were exposed and identified as near the suprasternal notch as possible. Identifying ligatures were placed on each but none were tied. The loose ends of the ligature were secured by hemostats.

From this point the dissection was carried along the vessels until a solid thrombus was found in the carotid artery at about the level of the cricoid cartilage. A former surgeon reported that ligation of the common carotid made no difference in the bleeding. As will be shown later, this phenomenon tends to substantiate the diagnosis of a primary thrombus in the common carotid. The separation of structures from here on was extremely difficult and sharp dissection was necessary. Just as the bifurcation of the common carotid artery was located, there was a very profuse flow of blood. Blood poured from the wound, through the fistula into the throat and even from the ear. Pressure controlled the bleeding while the external carotid and internal carotid were identified. A ligature was placed around both the external and internal carotid arteries and the bleeding was effectively controlled. Both arteries were filled with pulsating arterial blood. It was noticed at the operation, and had been noticed previously, that blood pressure changes were unusual. The bleeding was now under control and as the bifurcation of the common carotid was dissected a laceration was discovered.

Part of the vessel wall was necrosed and it was in this necrotic area that an erosion had taken place. The location approximated the carotid body. Any tension in this area would cause the blood pressure to drop. Relaxing the tension caused a rise in blood pressure. The ligatures around the external and internal carotid arteries were tied, and the bleeeding was permanently controlled.

Recovery was complicated by a plastic operation which the local use of sulfathiazole made more difficult. Hardened, stony masses in the neck, covered by bleeding granulations, rendered an ordinarily simple procedure one of extreme annoyance. The solidified masses of powder were carefully removed. Patience being demanded and annoyance being controlled, an acceptable closure was done. The patient is now a robust girl and completely recovered. She has a pair of tonsils which must be removed soon and I do not relish the job.

COMMENTS

1. A primary common carotid thrombosis is reported and, in this instance, was probably due to a suppurating cervical gland.

2. Sulfathiazole powder may act as a foreign body when used locally.

121 East 60th Street

XVIII

MENINGITIS, UREMIA, AND DEATH*

MARVIN F. JONES, M.D.

NEW YORK CITY

This patient was 68 years old. He was a grand gentleman, a good sport and had a sense of humor that made his death from meningitis and uremia more than one of scientific failure. Of course, it is only the advent of the sulfa drugs that gave us even an excuse for hope. His chief complaint was a severe, continuous frontal headache of two weeks' duration. This headache continued unchanged until his death. His right ear had troubled him for about the same length of time and myringotomies had been done. Sulfa powder, probably sulfathiazole, had been used in the ear. The ear was healed when I first examined him. There had been a transient vertigo with intermittent fever. During the three days previous to my examination, he had developed constant hiccoughs, projectile vomiting, irrational moments, tremendous abdominal distension from flatus and bladder retention of urine. Very little of diagnostic value was found on my first examination. The abdominal reflexes were absent; this absence might have been the result of extreme distension. The deep reflexes of the left leg were exaggerated. A questionable, spontaneous Babinski reflex was present on the left. The patient hiccoughed continuously but there was no vomiting. My guesses at this time were: (1) meningitis, (2) frontal lobe abscess, (3) encephalitis. A neurological examination was made. The report was as follows: Finger to nose test is inaccurate; there is transient oscillatory nystagmus to the left. The right palpebral fissure is greater than the left. There is a slight droop to the right corner of the mouth and both disks are hyperemic. Weber is referred to the right ear. The left patellar reflex is greater than the right, the contralateral patellar reflex is left to right, the plantar reflex is poor on the left. The neurologist's opinions were: (1) right frontal lobe disease, (2) meningitis, (3) brain abscess.

An urologist was called and introduced a self-retaining catheter into the bladder which he left in place because of the difficulty encountered in catheterization.

*Presented before the Eastern Section Meeting of the American Laryngological, Rhinological and Otological Society, Hartford, Conn., January 15, 1943.

The spinal tap told the story. The fluid was turbid and under 340 mm. pressure, contained three plus albumen, three plus globulin, 2740 cells, polymorphonuclears 85 per cent, and a few short chain, gram positive cocci. A culture produced a pneumococcus type three.

This patient had been on sulfadiazine previous to admission and this drug was increased in dosage and continued. Daily spinal punctures were done to relieve spinal pressure and furnish fluid for the sulfadiazine estimation. Surgical intervention was considered and rejected because of the following items: objectively, the right ear had resolved; and there was a conflicting opinion regarding the interpretation of the roentgenograms.

The roentgenologist reported the right mastoid as large and cellular. The cells extended slightly into the zygoma; the sinus slightly forward. The cells, which were all fairly large, contained granulations and possibly some exudate. There was evidence of some early softening in the deeper cells between the sinus, the posterior canal wall and the antrum. The petrous pyramid was noncellular on both sides. On the sinuses the roentgenologist reported a chronic sinusitis involving both ethmoids, especially marked posteriorly, and slight involvement of both antra.

The age of the patient, his critical condition, the absence of diagnostic, localizing data plus the absence of noticeable or perhaps more definite signs of destruction in the mastoid as seen in the roentgenograms, the frontal lobe symptoms with radiographic opinions of chronic sinusitis left very little hope that surgery on the right mastoid would help and every reason to believe the patient would not survive during the operation.

Two comments of the physician in charge should be quoted. "It seems noteworthy that the sulfadiazine concentration in the spinal fluid could be kept so nearly that of the blood." In one instance, the spinal fluid content exceeded that of the blood. The physician's second remark was, "It is also noteworthy that in spite of this satisfactory cerebrospinal fluid level there was practically no effect on the cerebrospinal pressure or cell count." His final comment is in the nature of philosophy: "Even though this renal damage was contributed to very largely by the heavy dosage of the drug, nevertheless, we could not do less in a condition which, without adequate dosage, has always proved one hundred per cent fatal." This patient was under my care seven days. It seemed much longer.

COMMENT

1. The miracles of the sulfa drugs must be carefully watched or the human tendency to procrastinate in using necessary surgery may react unfavorably on our mortality rates.

121 East 60th Street

XIX

RHINOLITH

H. B. Stauffer, M.D.

Jefferson City, Missouri

The formation of nasal calculi or concretions is fairly rare and a review of the literature indicates that they are becoming less numerous because of better nasal hygiene and more frequent nasal examinations. Hippocrates doubtlessly encountered rhinoliths, for he wrote of something in the nose which when touched with a probe sounded like stone, according to Wright.[1] Hippocrates sometimes recommended an external incision for removal and advised postoperative application of copperas powder and the insertions of tents in the nostrils smeared with oil and honey. The ancients developed the sponge method of removing nasal polypi and foreign bodies. This consisted of tying a sponge to a piece of string and pulling it through the nostril into the pharynx.

Concretions are found more often in adults than in children and more often in females than in the male, according to Thomson,[2] Morwitz,[3] and Snyder and Feldman.[4] Rhinoliths are divided into true rhinoliths, those formed around a nucleus of blood and mucus, and false rhinoliths; that is, a deposit of inorganic salts formed around a foreign body such as a bead, a sponge, a button or a piece of coal. They vary in size from that of small granules to gigantic masses completely obstructing the nasal chamber. The largest recorded weighed 110 grams. Myerson[5] reported a rhinolith weighing 56 grams which had to be removed by lateral rhinostomy. Some three hundred cases were recorded prior to 1921. Twenty-one cases were reported between 1925 and 1936 according to Snyder and Feldman. Since 1936, eight additional cases are on record as found listed in the "Quarterly Cumulative Index Medicus." Green[6] reports a case of a man, aged 41, who had no symptoms except "stuffy" ears. One by Costen[7] occurred in a case of nasal diphtheria. Hutcheon[8] also recently reported a case of rhinolith combined with cholesteatoma of the maxillary antrum. The most recent case was reported by Goodyear[9] in 1942.

Barnhill[10] points out that in the differential diagnosis, syphilitic sequestration, calcified polypi, osteoma, necrotic bone, malignancy and chronic sinusitis must be considered.

CASE REPORT

Mrs. T. W. J., married, aged 63 years, was seen in consultation on May 26, 1942, complaining of pain, tinnitus and an occasional cracking noise in the left ear which had increased in severity the past three months. She also gave a history of excessive lacrimation from the left eye and pain around the orbit on the left side only during attacks of acute upper respiratory infections. The latter symptoms could definitely be traced back for a period of fifteen years to an attack of influenza but she had never been examined by an otolaryngologist during this period. There was no history of epistaxis.

The family history was negative and there was no history of a previous nasal operation or foreign body in the nose. The blood Wassermann was negative. The left external ear canal was negative and the drum membrane on each side was moderately retracted. Examination of the nose revealed the left nostril obstructed by a hyperplastic inferior turbinate with granulation tissue near the septum and deviation of the septum to right. There was very little foul nasal discharge present. When the mucous membrane was cocainized and the interior of the nose palpated with a probe a hard, bone-like, immobile substance was felt beneath the granulation tissue. Further examination revealed a nasal concretion resting upon the floor of the nose and completely molded around the inferior turbinate. The V-shaped depression in the concretion represented the inferior turbinate. The concretion extended upward and backward against the middle turbinate and there was evidently pressure in the region of the sphenopalatine ganglion which may have accounted for the pain in the ear. The eustachian tube apparently was not obstructed because the concretion did not extend far enough backward. The medial half of the hard, brittle mass was cracked with a bone forceps and removed anteriorly, the remaining portion beneath the inferior turbinate was then pushed into the pharynx and obtained orally. After extraction there was considerable hemorrhage and the left nostril had to be packed for 48 hours. The patient was put on a bland oil spray and the secretions aspirated with suction every other day until healing took place about the seventh day. The left maxillary antrum was negative at this time.

Chemical analysis[11] revealed that the concretion consisted of calcium phosphate and carbonate. There was a slight xanthoproteic

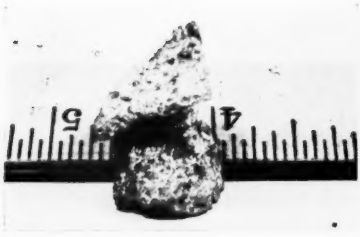


Fig. 1.

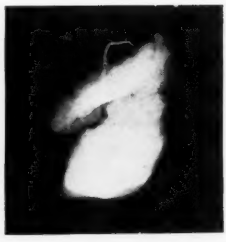


Fig. 2.

Fig. 1.—Photograph of rhinolith showing its size.

Fig. 2.—Roentgenogram of rhinolith after its removal.

reaction for protein. The analysis was negative for oxalate, urate, magnesium and the NH_4 group. The weight of the concretion was 100 grains (6½ grams). The x-ray was negative for any foreign body. The concretion was grayish white in color, rough on all surfaces and quite brittle.

Examination six months later revealed marked atrophy of the inferior turbinate, a normal septum, normal hearing in either ear, and negative sinuses. Blood pressure was 180/90. Tinnitus and pain in the left ear have been absent since the operation.

SUMMARY

1. Rhinolith is a fairly uncommon condition occurring in but few instances in one's practice of many years.

2. Many cases reported in the literature complained of excessive unilateral lacrimation due to the obstruction of the nasolacrimal duct.

3. Some case reports emphasize the fact that frequent head colds may be a factor in formation, while other authors emphasize the fact that lacrimal secretions cause more concretions than nasal secretions.

4. True rhinoliths are rare since most form about a foreign body of some type.

5. True rhinoliths are usually of long standing. All rhinoliths are unilateral and no reports of reccurrence are on record.

6. Large rhinoliths may have to be removed by lateral rhinostomy.

CONCLUSION

A true rhinolith is reported which apparently existed for over 15 years causing no nasal symptoms except blocking of the naso-lacrimal duct during head colds. The symptoms which caused the patient to consult a physician were entirely referred to the ear.

234 MADISON STREET

REFERENCES

1. Wright, Jonathan: A History of Laryngology and Rhinology, Philadelphia, Lea & Febiger, 1914, pp. 57, 58.

2. Thomson, Sir St. Clair: Diseases of the Nose and Throat, New York, D. Appleton-Century Co., 1937, pp. 159, 160.

3. Morwitz, S. M.: Rhinolith, Arch. Otolaryng. 20:704-707 (Nov.), 1934.

4. Snyder, J. and Feldman, M.: Rhinoliths: Report of Three Cases with a Review of the Literature, ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY 45:430-435 (June), 1936.

5. Myerson, M. C.: Rhinolith, Requiring External Nasal Operation for Removal, Laryngoscope 38:393-395 (June), 1928.

6. Greens Eye Hospital, San Francisco, Calif.: Bulletin of Pract. Ophth. 9:39 (April), 1939.

7. Cosген, J. B.: Nasal Diphtheria, Four Cases, One with Rhinolith, J. Mo. Med. Assoc. 36:266-268 (July), 1939.

8. Hutcheon, J. R.: Rhinolith Combined with Cholesteatoma of Maxillary Antrum, Med. J. Australia 1:451 (April), 1941.

9. Goodyear, H. M.: Rhinolith, Case Report, Cincinnati J. Med. 23:33-44 (March) 1942.

10. Barnhill, J. F.: The Nose, Throat and Ear, New York, D. Appleton and Co., 1928, p. 56.

11. Mattice, M. R.: Chemical Analysis of Specimen, New York Post-Grad. Med. School and Hosp. Chem. Lab. Technician, New York City, Dec. 15, 1942.

XX

CARCINOMA OF THE MIDDLE EAR AND MASTOID*

LEWIS T. BUCKMAN, M.D.

WILKES-BARRE, PA.

It is evident from a study of the literature that carcinoma of the middle ear and mastoid occurs infrequently, that it masks itself by simulating other more common abnormalities of these parts and that for these reasons it may be missed in the initial stages. In addition, treatment, in common with treatment of carcinoma of other parts, has not yet standardized itself nor assured itself of success sufficiently to permit a sense of repose to the practitioner in the smaller cities and smaller clinics who may have had, or may expect to experience, the first and only case which statistics indicate is probably the allotment for his lifetime. For these reasons, a discussion of the problem and the outline of a case with unfortunate outcome, would seem to be worth our time and attention.

REPORT OF A CASE

A female, 47 years old, having had a discharging right ear over a period of 15 years, presented herself with a homolateral facial paralysis of five days' duration. This was accompanied by mild vertigo and pain.

On December 15, 1941, there was a scant discharge from the right ear with a foul odor. Granulations appeared on the posteroinferior wall just external to the remnants of the tympanic membrane and annulus. The middle ear was wide open; the mucosa, bathed in foul pus. With the intact left ear occluded by a noise apparatus, the right ear was completely deaf.

Roentgen examination of the mastoid region showed: "The right mastoid region including the antrum is densely sclerotic with no evidence of pneumatization. No evidence of abscess formation or cholesteatoma is noted. The sigmoid sinus is clearly visualized. The external auditory canal appears clear. The left mastoid region is similarly affected but is not so densely sclerotic as the right. No

*Presented at the Eastern Section Meeting of the American Laryngological, Rhinological and Otological Society, Hartford, Connecticut, January 15, 1943.

evidence of destruction of the petrous pyramids is noted. Impression: Bilateral sclerotic mastoiditis; the right side is more involved than the left."

On admission to the hospital, the temperature, the pulse and the respiration were normal, and the routine blood and urine examinations showed no abnormalities.

Operation December 16, 1941, consisted of exposure of the right mastoid process by the postauricular route. The mastoid cortex measured 1.5 cm. of solid bone. The only cellular developments were a tract at the tip, along the posterior canal wall approaching the tympanum, at the angle back of the horizontal semicircular canal, and at the extreme posterosuperior angle of the mastoid process. The structures of the middle ear had been destroyed, together with the greater part of the tympanic membrane and the annulus. The middle ear was filled with cholesteatoma-like material. There was tissue described at the time as "granulations" along the mastoid aspect of the canal wall, which unfortunately was not taken for histological examination. No exposure of the facial nerve was observed.

What was considered at the time to be an adequate radical mastoidectomy was done, and skin flaps were laid down from the canal in the usual manner. The postauricular wound was closed.

There was primary healing of the skin wound, but there was profuse postoperative discharge from the ear with pain radiating to the right temple, usually nocturnal. Bacillus pyocyaneus and hemolytic staphylococci were reported from the pus. Sulfathiazole, gm. 1.5 every four hours, produced a surprising cessation of discharge within 48 hours and with it, relief from the pain. Sulfathiazole was continued in decreasing dosage for four weeks. The facial paralysis persisted.

Two weeks later she had renewed purulent discharge with recurrence of homolateral temporal pain. Eleven days later, she had two attacks of vertigo with vomiting, the discomfort lasting for a period of 20 hours.

X-ray examination February 18, 1942, on readmission to the hospital showed: "A small sclerotic nonaerated mastoid bilaterally with no cells beyond the periantral triangle; an oval-shaped bone defect just posterior to the right periantral triangle (postoperative); sclerosis of the petrous pyramids in the lateral halves, but no definite areas of bone necrosis."

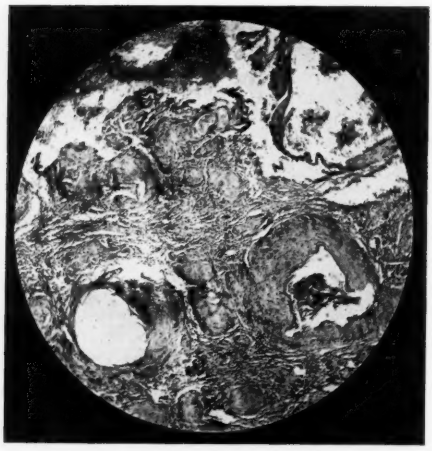


Fig. 1.—Photomicrograph of section of specimen, x30.

The temperature and pulse were normal. The white blood cells were 10,800 with 80 per cent polymorphonuclears.

With the recurrence of purulent discharge from the ear after the first hospitalization and subsequent to the course of sulfathiazole, there appeared at the inner end of the canal, and blocking the opening to the operative cavity from the canal, a mass of tissue. This had not the appearance of typical granulation tissue. It was grayish; it came off in chunks when probed or curetted; it was friable and bled easily, although the bleeding was as easily controlled. It recurred, and it recurred with exuberance. We were then reminded of the "granulation" tissue seen at the first operation along the mastoid aspect of the posterior canal wall, not in the canal, which had appeared unusual and had given pause in the first operation, but which had not been submitted to the laboratory.

The cavity was reopened on February 19, 1942, two months after the first operation. The old cavity was found filled with a friable tissue which broke off in chunks and bled readily. It was obviously neoplastic and specimens were sent to the laboratory. The bone was clean but strangely soft. The facial ridge was now gone and on the depth of the wound lay the nearly severed remains of the

facial nerve. There was a pathological fracture of the remains of the floor of the middle ear and the bony canal.

Even without laboratory verification, we felt convinced we were dealing with a neoplasm. We realized we had lost two months' time; the pathological fracture suggested invasion already accomplished beyond limits controllable by excision, and we consequently packed and closed the wound lightly.

The pathologist reported as follows: "Microscopic examination: Section shows the specimen to be made up of a fibro-areolar stroma in which are embedded numerous sheets of slightly anaplastic and hyperchromatic epithelial cells. There is a definite tendency toward pearl formation. Diagnosis: epithelioma, grade 2."

The patient was referred for x-ray treatment and received the following schedule of doses: "A total of 3570 r (measured in air). Treatment was administered over a 22-day interval from March 3, 1942, to March 25, 1942. The following factors were employed: 200 kv., 25 ma., 50 cm. distance skin portal, 8 cm. circular, filtration 7/10 cu. 1.0 al. A marked radiation dermatitis was obtained at the site of treatment, which reached its maximum about five weeks from the time of the initial treatment."

She left the hospital March 14, 1942, and within a week had dysphagia because of involvement of the pharyngeal constrictors. Three months later there were visible tufts of recurrent neoplasm in the canal and mastoid cavity; extension had progressed to the glenoid fossa and parotid region. Pain became more and more marked. External ophthalmoplegia developed, cachexia made its appearance, and death mercifully intervened on August 24, 1942.

An analysis of published reports is purposely omitted. This form of medical plagiarism to not a few of us seems only to confuse the clinical description. Since one man's experience with carcinoma of the middle ear and mastoid is usually quite limited, it must be assumed that what he may say about the disease in a published paper is largely what he has understood from the composite picture obtained by a study of the published reports of others. There have been sufficient reports, especially in recent years, to verify what one can assume to occur clinically from his knowledge of carcinoma in more frequent occurrences elsewhere in the body. A list of these references is appended to the paper. Few direct references will be made to them in the body of the paper. There is no priority in recognition of the disease, nor in forms of treatment, which need to be acknowledged, except as noted later.

Fig. 2.

Fig. 3.

Fig. 2.—Roentgenogram showing the appearance of the left mastoid.

Fig. 3.—Roentgenogram showing the appearance of the right mastoid.

This discussion has to do with carcinoma of the middle ear and mastoid only. It has no reference to malignant lesions arising on the pinna or on the face or in the scalp near the ear and extending to the ear, or to lesions of the canal external to the isthmus subsequently involving the middle ear.

Published statistics from large clinics indicate that carcinoma of the middle ear occurs in variable frequency from once in about 4,000 cases to none in 20,000 cases. In the series where the present case was observed, the records have been classified only since 1926. In this period of time, 1,200 cases of diseases of the ear have been listed and the present case is the only one of carcinoma of the middle ear.

It is usually preceded by a long period of otorrhea. One hypothesis to explain its occurrence is based on the supposition that the chronic discharge acts as an irritant to produce malignant changes in the mucosa of the middle ear, or in the skin of the external auditory canal which extends into the middle ear. Guttman[7] asks why we blame irritation of chronic discharge when there are so many chronic discharging ears that never become malignant. Thus chronic otorrhea may not be the causative factor, but may be of interest only because it is the indication for an operation and thus invites the

interference which discovers the cancer. Finally, it may well be the otorrhea which masks the cancer until the latter is well advanced. For these reasons, chronic otorrhea should assume a new significance.

Everyone has had the patient ask him of this or that, "Doctor, will this cause cancer?" The present-day American population reads health columns, listens to the radio, and is constantly exposed to health talks not alone by nurses and public health officials, but by the organized medical profession itself. Consequently cancer-minded patients are quite justified in asking such a question. We may be secretly amused by the trivia which patients sometimes build up in their minds as cancer-connected, but no otologist who has stumbled on a case of cancer in a chronic otorrhea will ever again laugh off chronic otorrhea as of no consequence. And what is more to the point, enough of us have had that experience to warrant the dictum that chronic discharging ears should not be allowed to go indefinitely, especially in these days when conservative measures aided by the sulfa drugs produce beneficial results in a reasonable time on an uncomplicated chronic infection.

The development of homolateral facial paralysis in a case of carcinoma of the middle ear occurs frequently enough to warrant listing this as a symptom. In a case of chronic otorrhea, the development of homolateral facial paralysis is usually sufficient indication for operative interference. The point to remember is that enough observers have recorded facial paralysis to occur with carcinoma to remind us of the need to expect carcinoma when opening a mastoid process, which has been the seat of chronic otorrhea and in which facial paralysis has lately developed. This has been emphasized in the present case.

The third thing to remember is that not all excrescences from the middle ear associated with chronic otorrhea are aural polyps. Other observers have described these excrescences as being tougher than polyps; our own description would be the opposite. Under our observation, the growth came away in chunks and granules when wiped from the inner end of the canal. The bleeding was more prompt, but as easily controlled as from a polyp. There was a peculiar friability not generally observed in an aural polyp which aroused suspicion in a growth which recurred after the first operation, as has been recounted. In the references studied, only one other observer described the polyp-like tissue as grayish.

Pain is described as occurring late. In the present case, it was almost simultaneous with the appearance of the facial paralysis.

Certainly it had become evident within a week after the first operation.

The x-ray examination is said not to be helpful. This was verified by our experience.

As for treatment, the only conclusion one can derive from published reports, especially the older reports, is that treatment has been unsatisfactory. Radical excision or electrodesiccation to be followed by x-ray or radium treatment, has been advised, and the results generally appear bad. In 1930, Fraser[5] described his sleeve operation on the canal and the postoperative use of radium. He said that the prognosis is good in isolated ulcer of the external acoustic meatus with the sleeve operation; that even if the tympanum is involved, radium added to this makes a good prognosis; but that if the mastoid is involved, there is little or no hope.

Later in 1935, Schall[12] described his technique of wide removal of the entire cutaneous canal, radical mastoidectomy, and irradiation, with favorable results.

All this may be so where a pre-operative diagnosis has been made but one's efforts may be materially limited where there has been no suggestive manifestation in the canal and the malignant disease is discovered only on opening the mastoid process.

83 South Franklin Street

REFERENCES

1. Barnes, E. B.: Carcinoma of the Ear, Proc. Roy. Soc. Med. 23:1231 (June) 1930.

2. Bowman, R. J.: Carcinoma of External Auditory Canal, Middle Ear and Mastoid, Annals of Otology, Rhinology and Laryngology 49:225, 1940.

3. Burton, F. A.: Epithelioma of Middle Ear and Mastoid: Report of a Case, Laryngoscope 27:755 (Oct.) 1927.

4. Carbarrouy, J. E.: Epitheliomas of the Middle Ear and Cholesteatoma, Rev. de Laryng. Otol. Rhinol. 59:724, 1938.

5. Fraser, J. S.: Malignant Disease of the External Acoustic Meatus and Middle Ear, Proc. Roy. Soc. Med. 23:1235 (June) 1930.

6. Furstenberg, A. C.: Primary Adenocarcinoma of the Middle Ear and Mastoid, Annals of Otology, Rhinology and Laryngology 33:677 (Sept.) 1924.

7. Guttman, M. R.: Primary Carcinoma of the Tympano-Mastoid with Report of a Case, Ill. Med. J. 56:150, 1929.

8. Newhart, Horace: Primary Carcinoma of the Middle Ear: Report of a Case, Laryngoscope 27:543 (July) 1917.

9. Peele, J. C. and Hauser, G. H.: Primary Carcinoma of the External Auditory Canal and Middle Ear, Arch. Otolaryng. 34:254 (Aug.) 1941.

10. Robinson, G. Allen: Malignant Tumors of the Ear, Laryngoscope, 41:467 (July) 1931.

11. Rosenwasser, Harry: Neoplasms Involving the Middle Ear, Arch. Otolaryng. 32:38-53 (July) 1940.

12. Schall, L. A.: Neoplasms Involving the Middle Ear, Arch Otolaryng. 22:548-553 (Nov.) 1935.

13. Scott, Philip: Discussion on Malignant Disease of the Ear (Excluding the Pinna), Proc. Roy. Soc. Med. 32:1087 (July), 1939.

14. Spencer, F. R.: Malignant Disease of the Ear, Arch. Otolaryng. 28:916-940 (Dec.) 1938.

15. Stokes, H. B.: Primary Malignant Tumors of the Temporal Bone, Arch. Otolaryng. 32:1023, 1940.

16. Ullmann, H. J.: Treatment of Ear Malignancies, Cal. & West. Med. 37:369 (Dec.) 1932.

17. Whitehead, A. L.: A Case of Primary Epithelioma(?) of the Tympanum Following Chronic Suppurative Otitis Media, Proc. Roy. Soc. Med. 1:34, 1907-1908.

18. Yates, E. C.: Primary Carcinoma of the Middle Ear, Kentucky Med. J. 34:501, 1936.

XXI

TOXIC REACTION TO NUPERCAINE*

LEON L. TITCHE, M.D.

AND

WILLIAM H. CRAYS, M.D.

OTEEN, N. C.

While the literature is replete with accounts of undesirable reactions following the use of nupercaine, in the majority of cases the drug was employed for local infiltration or spinal anesthesia. Since idiosyncrasy following topical application of the drug appears to be infrequent, this case is being reported.

Nupercaine is the hydrochloride of alpha-butyl-oxy-cinchoninic acid diethylene-diamide and is a quinoline derivative. Various observers[3, 13] have reported its toxicity as being from three to five times as great as cocaine, and others[6, 7] have shown it to be from one-half to twenty times as toxic as procaine. Its analgesic action has been reported to be ten times stronger than cocaine[10, 13] and twenty times that of procaine.[10] Nupercaine, when injected, produces vasodilatation at the site of injection and Schlaepfer[10] states that a given amount of the drug in high concentration is much more toxic than the same amount in large dilution, since absorption into the blood is more rapid in the first instance. Benedict[11] reports that nupercaine is the most toxic of all local anesthetics, though Gorrell[4] states that if the solution is not injected into the blood stream, no serious accident will occur. Tovell[12] warns that symptoms may develop if the application of the drug as an ointment is repeated over several days and Fanburg,[1] Fowlkes,[2] and Hailey and Hailey[5] report cases of dermatitis due to the use of nupercaine ointment. In one case Perera[9] noted marked edema of the eyelids and conjunctiva following instillation of nupercaine solution into the conjunctival sac. Bone and Bloom[3] find that absorption of nupercaine after topical application is relatively slow and Gatewood[3] reports excellent results in the use of the drug both topically and in local infiltration in rhinolaryngology without any ill effects. Schlaepfer[10] mentions two patients in whom hysterical

*Published with permission of the Medical Director, Veterans' Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

stages of excitement occurred a few hours after intraspinal administration of nupercaine. Subsequently there was complete amnesia for these events. Organe[5] reports the occurrence of convulsions in three cases following infiltration anesthesia, one of these ending fatally. A review of the files of the Ciba Pharmaceutical Products Company, who manufacture the drug, does not reveal a similar occurrence or even one that resembles this case.

Because of the potency of the drug only small amounts in dilute solution have been recommended for anesthesia. For spinal anesthesia the strength of the solution has varied from 1:1500 to 1.200, employing about 2 mg. per kilo of body weight, and using not more than 7.5 to 10 mg. of the drug. For local infiltration a 1:1000 solution has been recommended and the amounts not to be exceeded have varied from 50 to 100 cc. For topical anesthesia, dilutions of 1:500 to 2½ per cent have been employed.

Since July, 1936, nupercaine has been employed for topical anesthesia of the eye, the nose, the pharynx and the larynx in 547 cases at this hospital. This is the only one in which a reaction has been encountered.

REPORT OF A CASE

C. S. D., colored, male, aged 44, with an irrelevant family history was admitted to this hospital on October 5, 1942, for treatment of pulmonary tuberculosis. There is an authentic history of the diagnosis of active pulmonary tuberculosis in 1919. He was hospitalized in government hospitals until 1925, at which time he was considered to have reached maximum benefit and was allowed to go home. Since then he has followed a rest regime and has done part time work as a waiter. During the intervals he has had a chronic cough and occasional chest pains. On two occasions he had what was thought to be influenza. He has never been robust and his highest weight was 125 pounds. During the past two years he has noticed an increase in the cough, easy fatiguability, and a gradual loss of weight. The cough is paroxysmal in nature, is increased at night when the patient is recumbent, and is productive of about one to two ounces of yellowish mucoid sputum. There has been no hemoptysis. Pain is localized over the left anterior chest and does not radiate. There have been no chills or fever nor any foul sputum. He presents no gastrointestinal symptoms or genito-urinary complaints. There is no history of allergic manifestations.

The physical examination on admission revealed a somewhat underdeveloped and poorly nourished colored male. His weight was

95½ pounds; height, 64 inches. His blood pressure was 134/86; temperature 98° F.; pulse 100. Except for a few fine posttussic râles in the right apex, the lungs showed no abnormal physical signs. A dorsal spinal scoliosis and a hydrocele of the cord, left, were the only findings of note on general physical examination.

The laboratory findings were as follows: red blood count 4,310,000, white blood count 10,750, polymorphonuclears 50, lymphocytes 37, monocytes 7, eosinophiles 6. The sedimentation index was 13 mm. in one hour. The urinalysis showed: specific gravity 1.026, sugar and albumin negative, no casts or red blood cells. The feces were negative for parasites. Ten routine smears and five twenty-four hour concentrated specimens of the sputum were negative for acid-fast bacilli. The blood Wassermann and the precipitation tests were negative.

The x-ray examination of the chest on October 6, 1942, revealed a small amount of fibroid deposit at the apex of the right lung and obliteration of the right costophrenic sulcus. These findings were interpreted as being the probable residuals of a previous tuberculous process. In addition, on the postero-anterior film, a margin of what appeared to be a rounded shadow could be seen projecting slightly beyond the cardiac border in the lower left lung. Oblique films taken on October 13 revealed a dense oval shadow 3 to 4 cm. in diameter lying behind the heart within the left lung.

In an attempt to localize the lesion, it was decided to instill a contrast medium into the left bronchial system. The patient accepted the recommendation and the night before was given phenobarbital gr. 1.5. On the morning of October 16 breakfast was omitted, barbital gr. 5 was given at 9 o'clock, codeine gr. .5 was given by hypodermic at 9:50 o'clock and the patient taken to the Eye, Ear, Nose and Throat Clinic in a wheel chair. Upon arrival in the clinic the pharynx was sprayed with approximately 2 cc. of 2 per cent nupercaine and 4 cc. of nupercaine were applied to the pyriform sinuses on a laryngeal applicator and instilled into the larynx and trachea through a cannula. About fifteen minutes were taken to do this. The cough reflex was abolished. All at once the patient began to tremble and then throw himself from side to side. He was semiconscious, as evidenced by response to commands, but soon he became unconscious and mild generalized convulsions began. Codeine gr. .5 was given hypodermically and, when no effect was apparent in ten minutes, morphine gr. .25 was given. The convulsions became somewhat less and the patient was placed on a stretcher and returned to

his ward. When he was put back to bed he was still unconscious and exhibited clonic convulsive movements of the entire body. Attendants were stationed to provide restraint. The clonic movements continued and examination showed no embarrassment of respiration and the heart remained regular with a good pulse volume. There was no outcry, no biting of the tongue, and no incontinence of urine or feces. The head rolled from side to side, the arms moved in flexion, and the legs were drawn up to the trunk. There was no suggestion of opisthotonus. The pupils were found to be miotic, but this was believed to be due to the morphine which had been given. Otherwise there were no ocular manifestations.

After fifteen minutes with no sign of cessation of the attack, scopolamine gr. 1/150 was given. Intravenous barbiturates were held in readiness, but since tonic contractions were absent and since considerable sedation had already been attempted, they were not used. The attack gradually weakened and subsided in about one hour, to be replaced by a deep sleep. The patient did not evidence consciousness until several hours later and then had no recollection of the previous events. He complained of some abdominal soreness and was hoarse for forty-eight hours. There was a febrile reaction on the following day, temperature 101° F., which subsided in seventy-two hours. No residual neurologic signs were evidenced.

To determine whether the patient was sensitive to the drug, one drop of 2 per cent nupercaine was instilled into the conjunctival sac near the outer canthus. After five minutes there was dilatation of the vessels and injection of the conjunctiva of the inferior half of the globe and of the lower lid. Eight drops of 2 per cent nupercaine were placed on a small piece of gauze and fastened to the flexor surface of the left forearm for twenty-four hours. There was no sign of reaction at this time.

Unfortunately it is not now possible to state the correct diagnosis of the pulmonary lesion. The previous x-ray films made of this patient in 1925 are no longer available, but interpretations of these films at that time make no mention of the lesion. Because of the fear that some occurrence similar to, or worse than, the attack herein described might result, the patient has refused bronchoscopy and other investigations under some type of brief general anesthesia.

SUMMARY

A case exhibiting marked idiosyncrasy to nupercaine has been presented. Toxic effects were noted after the administration of 6 cc.

of a 2 per cent solution, and after recovery, no deleterious effects were observed and there was complete amnesia for the occurrence. A review of the literature reveals no similar effects following the topical application of the drug.

VETERANS ADMINISTRATION

REFERENCES

1. Fanburg, S. J.: Dermatitis Due to Nupercaine, J. A. M. A. 101:30 (July), 1933.

2. Fowlkes, Richard W.: Dermatitis Due to Nupercaine, J. A. M. A. 100:1171 (April), 1933.

3. Gatewood, W. L.: An Effective Substitute for Cocaine and Procaine in Rhinolaryngology, Laryngoscope 42:3 (Dec.), 1932.

4. Gorrell, Ralph L.: The Nupercaine Treatment of Lumbago, Tristate Med. J. 11:2223 (Feb.), 1939.

5. Hailey, Howard, and Hailey, Hugh: Dermatitis Caused by Nupercaine, Arch. Dermat. and Syphil. 36:1084 (Nov.), 1937.

6. Keyes, E. L., and McLelland, A. M.: Further Experiences With Nupercaine, J. A. M. A. 96:2085 (June) 1931.

7. Lingenfelter, F. M.: Nupercaine Infiltration Anesthesia, J. Okla. State Med. Assn. 27:440 (Dec.), 1935.

8. Organe, Geoffrey: Convulsions Following Percaine Local Anesthesia, Lancet 243:33 (July), 1942.

9. Perera, C. A.: Ocular Sensitivity To Nupercaine, Arch. Ophth. 24:344 (Aug.), 1940.

10. Schlaepfer, Karl: Nupercaine Spinal Anesthesia in General Surgery, Anesth. and Analg. 18:26 (Nov.-Dec.), 1939.

11. Tennent, E. H.: Local Anesthetic Solutions, U. S. Naval M. Bull. 32:487 (Oct.), 1934.

12. Tovell, Ralph M.: Regional Anesthesia, The Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Co., 1939, p. 535.

13. New and Nonofficial Remedies, J. A. M. A. 116:74, 1941.

XXII

STAPHYLOCOCCUS MENINGITIS TREATED WITH SULFATHIAZOLE*

JOHN F. TOLAN, M.D.

SEATTLE

We might safely designate this particular period in medicine as the "sulfur-derivative era." There have been few acute infections in which one or more of these derivatives have not been used. Care has to be exercised at all times in their administration. The patient should be impressed with the dangers arising from the careless use of them. I feel that the patient should be in the hospital under constant observation during the period the drug is being administered.

It is interesting to follow the evolution of these drugs, starting with neoprontosil. The change has always been for the better, and each successive drug has its far-reaching advantages over the previous ones. The derivative in which I am interested at the present time is sulfathiazole. Forsbinder and his co-worker, Walter,[1] first reported the thiazole analogue of sulfapyridine; namely, sulfathiazole. They also instituted tests for the blood determinations of this drug. Sulfathiazole has rapidly replaced both sulfapyridine and sulfanilamide. It has accomplished results heretofore unheard of. In the past, so far as I have been able to determine, staphylococcus meningitis has in all cases been fatal. A recent case report by Cohen and Galpern[2] bore out our impressions regarding its use in this particular infection. Van Dyke,[3] in his work, proved that sulfathiazole was more rapidly absorbed than any of its fellow sulfanilamide derivatives. In other words, the blood concentration reaches the desired level in two to four hours. It was also found that it was excreted more rapidly. Rake and McKee[4] have shown in vitro and in mice that sulfathiazole is much more effective than sulfamethylthiazole, sulfapyridine, or sulfanilamide on staphylococcus aureus. He also brought out the fact that sulfathiazole is also an effective bacteriostatic and bactericidal agent against staphylococci.

Osgood[5] pointed out in his recent article on chemotherapy that the first important step is to decide whether the patient actually

*Presented as a candidate's Thesis to the American Laryngological, Rhinological and Otological Society.

needs the drug. Judicious care must be exercised in each individual case in determining the benefits to be derived as against the risk of giving the drug to the patient. Under the most careful observation, the mortality was still one per cent. By careful observation I mean the making of a daily white blood cell count as well as daily hemoglobin and blood-sulfathiazole determinations. It has been proven time and time again that sulfathiazole is superior to sulfanilamide against the beta hemolytic streptococcus. Likewise, it is equal or superior to sulfapyridine against pneumococcus. Many case reports show that it is very effective in the treatment of streptococcus viridans.

We, as otolaryngologists, appreciate the fact that in our field we are constantly dealing with many mixed infections. In view of the fact that sulfathiazole has proved to be so effective in these mixed infections, its use should be given preference over the parent drugs. Frequently neoarsphenamine is used with sulfathiazole and it has proved to be very effective against the staphylococcus organisms.

Briefly, the toxic effects of sulfathiazole are as follows: (1) a mild dysfunction of the blood-producing system; (2) a transitory oliguria; (3) frequent vomiting and psychosis; (4) hematuria. Reinhold[6] and his co-workers pointed out that sulfathiazole is rapidly absorbed in the gastrointestinal tract and is equally as rapidly excreted in the urine.

The suggested dosage varies from an initial dose of two to four grams followed by one to two grams every four hours around the clock.

The sulfathiazole blood level should be maintained between 5 mg. and 8 mg. per 100 cc. In those individuals who are unable to take the drug by mouth, the next choice in administration is through a nasal feeding tube. The latter method is the procedure that we used in the case I am to report. The drug can also be administered intravenously in the form of a sodium salt. In some instances, it has been given by rectum in a suspension of water. It is uniformly agreed that the drug should not be discontinued immediately after the temperature has reached normal. Instead, it should be administered for one week following the return of normal temperature.

Toxic manifestations due to the idiosyncrasies associated with the drug should be watched for when sulfathiazole is used. Many cases of continued elevated temperatures may be traced directly to the drug.

REPORT OF A CASE

Mr. G. K., a white male, aged 46, suffered an attack of "flu" on December 15, 1940, at which time he first noticed some stuffiness of his right ear. Associated with this, was a pain over the right eye radiating back over the mastoid region. The patient suffered no nausea nor vertigo. On December 24, a paracentesis was done. Very little discharge was obtained at the time. The patient stated that the otalgia was relieved but that the pain continued over the right eye and the right side of the head. Because of the discomfort, it was necessary to administer narcotics frequently. On January 15, the patient had a recurrent attack of influenza and was placed in a hospital for a period of three to four days. This time he was given sulfanilamide, but his symptoms did not improve. Because of the increasing periods of pain and the fact that the patient was having a large amount of purulent discharge from the right ear, consultation was advised, and I saw the patient for the first time on February 13, 1941.

The patient presented himself. He was a very emaciated person who was obviously, from his general appearance, suffering a great deal from pain. Just prior to admission, he informed us, he was unable to sleep at night even with narcotics because of the severity of the pain, which radiated from the right eye back over the mastoid region. The patient had no rigidity of the neck nor any signs of diplopia at this examination. His temperature was 99.4 F., his pulse rate 80, and his respiratory rate 24. The blood pressure was 110/80. The patient had marked tenderness over the right mastoid region, and the external canal was filled with a thick, creamy discharge. After cleansing the canal, we noted a small polyp which obstructed the view of the tympanic membrane. The remaining ear, nose, and throat findings were essentially negative. Neurological and ophthalmological examinations were likewise negative. Because of the ear findings and the distribution of pain, the diagnosis was made of mastoiditis complicated by a petrousitis, or the Gradenigo syndrome. The patient was hospitalized at this time.

X-ray examination of the mastoid showed a generalized clouding of all the mastoid cells, particularly in the region of the mastoid tip. The Towne position disclosed a rather large area of destruction in the right petrous apex. Examination of the blood showed the hemoglobin to be 120 per cent, red blood cells 5,520,000, and white blood cells 10,550. The urine examination was essentially negative. The patient was advised to have a right mastoidectomy.

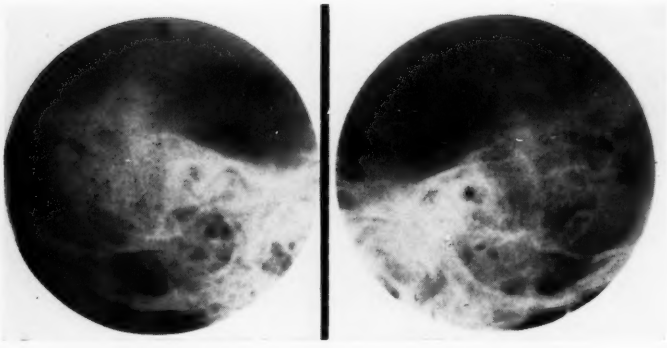


Fig. 1.—Roentgenograms right and left mastoids.

At operation, we found a large coalescent mastoid with a serous type of discharge throughout. I was very much surprised at not finding a greater degree of purulent discharge in the mastoid cavity. There was marked destruction of the mastoid tip and the periantral region. There was also considerable involvement of the postsigmoid cells. The sigmoid sinus was uncovered at the knee and proved to be normal in appearance. The dura in the epitympanum was exposed and found to be entirely normal. The horizontal and posterior canals were well demarcated in an attempt to find a sinus tract leading back to the petrous apex. It was deep in the solid angle that I found a considerable amount of granulation tissue and what I thought to be a sinus tract to the petrous apex. While the granulation tissue was being removed, pus under pressure appeared. The mastoidectomy was terminated at this point, and the cavity packed with vaselinized iodoform gauze. It has been my feeling that after a complete mastoidectomy is done the majority of the cases of petrousitis will automatically clear up.

During the week following the mastoidectomy, the patient showed marked improvement in his symptoms. The culture made of the mastoid discharge proved to be staphylococcus hemolyticus. Twelve days after the mastoidectomy the patient was discharged from the hospital and was told to report every three days for mastoid dressings. The patient continued to have a rather profuse drainage from the mastoid wound, but he had no fever nor any of his former symptoms.

On March 15, approximately one week after the postauricular incision had healed completely and the normal landmarks returned to the drum, the patient had a recurrence of pain over the right side of the head. Associated with this, he had some nausea and vomiting and chills. His temperature was 101.8 F. The patient was again hospitalized. A blood culture was made, and it proved to be staphylococcus hemolyticus. The white blood cell count at this time was 14,000 with 90 per cent polymorphonuclears.

On March 16, his temperature rose to 105.4 F. rectally. General heart and lung examinations were essentially negative. He became irrational and incontinent, and he assumed an opisthotonos position. The patient was given 50 cc. of 50 per cent glucose without any improvement in the picture. Neurologically, the patient had positive Kernig, Babinski, and Brudzinski signs. The Queckenstedt test responded equally. A lumbar puncture was done at this time and 560 cells were found; 90 per cent of the cells were polymorphonuclears. The spinal fluid was colorless. With an initial pressure of 35 cm. of water, the final pressure was 18 cm. of water. The patient, of course, had the clinical signs and laboratory findings suggestive of suppurative meningitis. Because of the patient's condition, it was necessary to give him sulfathiazole through a nasal feeding tube. The dosage prescribed was 30 gr. every three hours. On March 17, the spinal puncture was repeated. This time, a very cloudy fluid was obtained; the initial pressure was 240 mm. of water. The cell count was 8,900 with 79 per cent polymorphonuclears and 21 per cent monocytes. Cultures of the spinal fluid proved to be staphylococcus hemolyticus. Lumbar punctures were done daily, and there was noted a gradual decrease in the number of cells in the spinal fluid with a trend toward normal. The fluid also changed in appearance from cloudy to clear. A transfusion of 500 cc. of whole blood was given.

The patient's general condition improved slowly. During the next four or five days, his temperature rapidly returned to normal. Five days after the instigation of sulfathiazole through the nasal feeding tube, we were able to discontinue this method of administration of sulfathiazole, and the medication was given by mouth. On March 21, the sulfathiazole dosage was changed to 30 gr. every six hours. The blood sulfathiazole on this date was 8.3 mg. per 100 cc. The patient at no time complained of being nauseated while taking the drug. On March 23, he recognized his family and carried on a conversation. From that date until the date of discharge, on April

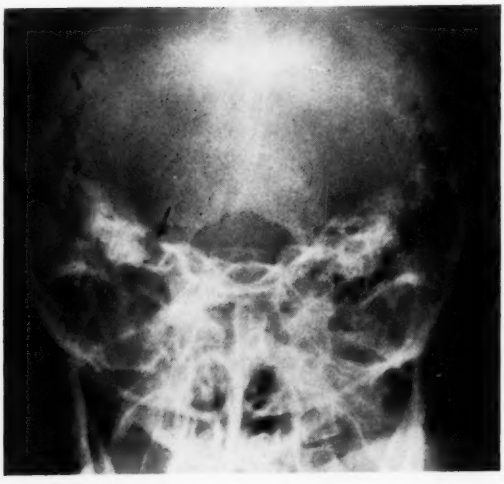


Fig. 2.—Roentgenogram, abscess of the petrous apex.

5, the patient showed progressive improvement. The sulfathiazole was discontinued on this date.

The patient has been seen on numerous occasions since his discharge from the hospital. He continues to do very nicely, and there has been no recurrence of his headaches.

The blood sulfathiazole reached a concentration of 8.7 mg. per 100 cc. The spinal fluid level did not at any time go beyond 2.5. Dr. Wesley C. Bowers[7] has pointed out that sulfathiazole should not be used in meningitis secondary to ear, nose, and throat infections because of its slow absorption in the spinal fluid. This is certainly true when sulfathiazole is compared with sulfanilamide and sulfadiazine; however, I feel certain that this case would not have survived without the use of sulfathiazole. One of the apparent causes for the failure of chemotherapy in most of these cases is the lack of the development of antibacterial antibodies on the part of the host. If this is the case, then some additional help must be obtained, such as the use of immune sera and immunotransfusions.

CONCLUSIONS

This patient showed complete relief of his symptoms following mastoidectomy. However, shortly after the mastoid incision healed, he had a return of the deep-seated pain. Undoubtedly, the infection in the petrous apex was being adequately drained through the mastoid, but when the sinus tract again became obstructed, his symptoms recurred. If the course of events leading to the meningitis had not been so fulminating, steps would have been taken to drain the petrous apex and relieve the headache. The abscess undoubtedly ruptured through the roof of the petrous apex into the posterior fossa, with resulting meningitis.

We must reiterate that our interest in sulfathiazole was stimulated by what impressed us as an almost unbelievable therapeutic result in what we feared was an incurable condition. Sulfathiazole proved to be more rapidly absorbed than any other sulfanilamide derivative. The blood concentration reached its highest level in one to three hours after injection. We now find, in recent experimentation, that the spinal fluid concentration does not reach the levels with sulfathiazole that it does with the use of sulfanilamide and sulfadiazine. Sulfathiazole is excreted more rapidly than the other sulfur-derivative drugs. Reinhold, Flippin, and Schwartz[6] contributed material on the disposition and action of the drug in man from the standpoint of pharmacology and toxicology. They found in their work that sulfathiazole was rapidly absorbed from the gastrointestinal tract and rapidly excreted in the urine, that the intravenous administration of a sodium salt results in almost complete quantitative excretion in the urine in 24 hours, and that the toxic effects are as follows: transitory and mild dysfunction of the blood-producing system, mild and only infrequent vomiting, and, in a few cases (less than three per cent), a dermatitis and psychosis. General caustic reactions from sulfathiazole are rare and mild. The suggested dosage for sulfathiazole is an initial dose of 3 gm. followed by 1 gm. every four hours. In this way, the concentration will vary from 1.2 to 9 mg. per 100 cc. of blood, with free sulfathiazole averaging about 5.45 mg. per 100 cc. of blood. The action upon staphylococcus is somewhat specific and, in spite of its failure to reach the spinal fluid in all the cases, the drug is extremely beneficial in the treatment of staphylococcus meningitis.

During the 25 years prior to 1936, only 76 recoveries from streptococcic meningitis were reported in the literature. Since 1936, more than 200 recoveries have been reported, and the mortality has dropped from 97 per cent to less than 35 per cent. We should always

bear in mind the fact that chemotherapy, when used in ear and nose infections, in many cases obscures the clinical picture and, in so doing, increases the danger of a sudden onset of grave complications; however, when meningitis complicating middle-ear infections has set in, then, of course, large doses of the sulfur-derivative drugs should be used, depending upon the type of organism with which one is dealing.

VIRGINIA MASON HOSPITAL.

REFERENCES

1. Forsbinder, R. J. and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines, J. Am. Chem. Soc. 61:2032 (Aug.), 1939.

2. Cohen, B. M. and Galpern, M.: Sulfathiazole for Treatment of Staphylococcic Meningitis, Arch. Otolaryng. 33:415-420 (March), 1941.

3. Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M.: Observations on the Toxicology of Sulfathiazole and Sulfapyridine, Proc. Soc. Exper. Biol. & Med. 42:410 (Nov.), 1939.

4. McKee, C. M., Rake, G., Greep, R. O., and Van Dyke, H. B.: Therapeutic Effects of Sulfathiazole and Sulfapyridine, Proc. Soc. Exper. Biol. & Med. 42:417 (Nov.), 1939.

5. Osgood, E. E.: Chemotherapy of Staphylococcic Infections, J. Pediat. 17:740-746 (Dec.), 1940.

6. Reinhold, J. D., Flippin, H. F., and Schwartz, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. 199:393 (March), 1940.

7. Bowers, W. C.: Infections of the Middle Ear and Nasal Sinuses, Bull. New York Acad. Med. 17:453-466 (June), 1941.

Society Proceedings

SIXTY-FOURTH ANNUAL CONGRESS

OF THE

AMERICAN LARYNGOLOGICAL ASSOCIATION

(CONTINUED FROM THE DECEMBER ISSUE)

A Case of Osteitis Fibrosa Cystica

JOHN D. KERNAN, M.D.

NEW YORK, N. Y.

This report concerns a young woman, 21 years of age, a Porto Rican, who had had a large firm swelling over the left eye for about a year. X-ray films showed it to be a cystic mass occupying both frontal sinuses, extending far back into the left frontal fossa and into the orbit on the left side. At operation it proved to be a cyst with thick fibrous and bony walls. This we eventually completely removed with a large part of the frontal bone and the floor anteriorly. The wound healed with considerable deformity. Histological examination of the tissue removed showed it to consist of partially absorbed bone and fibrous osteoid tissue containing calcified areas.

DISCUSSION

DR. THOMAS C. GALLOWAY: I would like to ask if there was any question of parathyroid disease.

DR. KERNAN: There was no evidence of parathyroid disease.

Granuloma of the Nose

(Case Report)

D. M. Lierle, M.D.

Iowa City, Iowa

The case of a young woman, 22 years of age, with so-called infectious granuloma or progressive lethal granulomatous ulceration of the nose is presented. The present illness and the various types of treatment are discussed.

DISCUSSION

Dr. Norton Canfield: I, too, had a similar experience during this past year, and in many respects this case is identical with the case I have had under observation in New Haven.

The patient was about ten years older than the patient that Dr. Lierle reported and had had a long-standing chronic suppuration in the maxillary sinus preceding the appearance of the granuloma. We were somewhat more energetic in our surgical removal of the sloughing and necrotic tissue, because we thought if we carried that out energetically it might be possible to put zinc peroxide in contact with the organism.

The only offending organism which we could find in our case besides the secondary invaders was hemolytic streptococcus. Complete sloughing of the upper lip and of the left side of the face took place and this patient developed inanition, secondary anemia, and terminal pneumonia.

As Dr. Lierle did, we tried every possible method to stop the infection and were entirely unsuccessful. We thought at one time that zinc peroxide was causing some recession, as Dr. Lierle thought in his case, but as things went on it was perfectly evident that it had no effect.

I have no further suggestions to make about the condition except possibly the use of an agent which is known as penicillin. I cannot tell you whether that drug is available but it is now being worked on in the laboratory of the National Research Council.

Dr. Mervin C. Myerson: This most unusual case recalls to my mind a tropical disease known as gangosa. Some fifteen or sixteen

years ago I had a case of gangosa in an American who had never been out of this country. It is entirely possible that Dr. Lierle is dealing with a case of gangosa in this instance, and I wonder whether he thought of that possibility. In gangosa there is no positive finding, but clinically it acts just exactly as Dr. Lierle's case did.

DR. ERNEST M. SEYDELL: I saw a similar case in consultation three or four years ago in a man of about 65 years of age. At the time I saw him his nose was entirely destroyed. The upper lip was not involved. The man lived about four or five months after I saw him and then died from a very severe hemorrhage. In this case everything was done that could be thought of without any effect at all.

DR. THOMAS C. GALLOWAY: I had a case which started in a similar fashion. I don't know how far it would have progressed, but I used energetic coagulating diathermy and I think that is the treatment of choice in such a lesion, at least when the lesion first occurs.

This is a type of anaerobic infection which becomes indurated and the induration inhibits the effect of the zinc peroxide. I wonder what kind of zinc peroxide you used and if it was properly activated. In such a lesion one must destroy every pocket beyond the limit of the infection and then zinc peroxide can be prophylactically employed to considerable advantage.

DR. LIERLE (in closing): In answer to the question with regard to the zinc peroxide, I want to say that it was properly activated. I think the fault was that we could not get into the deeper tissues early. I did not think of the disease, gangosa, which Dr. Myerson spoke about, but is there anything to do for it?

A Case of Vitamin Deficiency With Laryngeal Symptoms

R. L. GOODALE, M.D.

BOSTON, MASS.

(This paper appeared in full in the December 1942 issue)

A Case of Septic Thrombophlebitis of the Neck With Serious Complications

SAMUEL IGLAUER, M.D.

CINCINNATI, OHIO

A woman, aged 32 years, gave a history of sore throat of two weeks' duration accompanied by severe chills and high fever during the second week.

On admission, the tonsils were found to be inflamed and the left tonsil was displaced toward the midline. There was a tender indurated area along the medial border of the left sternomastoid muscle; there were also signs of consolidation in the left lower lung field.

At operation the anterior jugular vein was found to be thrombosed. It contained pus but no blood. The internal jugular vein was ligated (prophylactic), and subsequently the left tonsil was removed. Fever continued with the development of an empyema in both chests. The right chest was opened and drained. Subsequently, open drainage was instituted in the left chest. Several secondary operations on the chest were necessary.

The patient made a complete recovery after a hospital stay of 133 days. The author attributes the patient's recovery to repeated surgical interventions combined with chemotherapy.

DISCUSSION

DR. F. W. DIXON: In 1937 when I was visiting the clinic of Dr. Claus, of Berlin, he made use of a wide and free incision. The amount of thrombosis found was not always extensive. After finishing his neck dissection, he immediately removed the tonsil.

DR. T. E. CARMODY: What position did you put the patient in? Did you operate in the Trendelenburg position or did you elevate the foot of the bed to keep the infection from traveling downward?

DR. IGLAUER: With regard to what Dr. Dixon said, Dr. Claus, according to the last paper of his that I have read, has changed his procedure a bit inasmuch as he does not always remove the tonsil after operation on the neck, chiefly because these patients are very ill

and, if one takes out the tonsil, one interferes with their swallowing and nutrition.

In this particular case, however, it would have been advisable to remove the tonsil right at the operation. We intended doing that but we were somewhat delayed because of some bleeding in the neck, so we decided to postpone it.

As to Dr. Carmody's question, the involvement of this patient's lung was undoubtedly through the blood stream, so I do not see that posture would have had any effect. I think the patient came in with emboli in the lung. The first provisional diagnosis was pneumonia, or at least that was one of the diagnoses. She had had a thoracotomy.

DR. JOHN F. BARNHILL: Where did the original infection come from, from the tonsil?

DR. IGLAUER: It was peritonsillar.

DR. BARNHILL: Did she have quinsy to begin with?

DR. IGLAUER: Apparently, because as the tonsil was being removed the pus came out from the peritonsillar or pharyngomaxillary region, since the neck was already open. The exploration in the neck showed no pus.

DR. BARNHILL: What is the relation of the quinsy to a pharyngomaxillary abscess? Did the patient have a pharyngomaxillary abscess during the progress of this condition?

DR. IGLAUER: I think a quinsy is usually the source of a parapharyngeal abscess or pharyngomaxillary abscess.

Histoplasmosis of the Larynx

(Case Report)

L. W. DEAN, JR., M.D. (By Invitation)

ST. LOUIS, MO.

This is a report of a middle-aged teamster with a severe progressive ulceration of the larynx and the epiglottis which proved, on biopsy, to be histoplasmosis. Treatment with antimony and x-ray was ineffectual.

Résumé of Case Reports Presented Since 1939: Results and Present Status

CHARLES J. IMPERATORI, M.D.

NEW YORK, N. Y.

The first case report is that of a patient presented in 1939 and again in 1940 at the Annual Meeting of the Americal Laryngological Association held at Rye, New York. [Trans. A. L. A. 1939, p. 257; Trans. A. L. A. 1940, p. 47.]

This young man, who is now 22 years old, has a stenosis of the larynx. He appears to be in perfect health. He is six feet in height and weighs 185 pounds. He works as a machine operator 36 hours weekly.

The stenosis resulted from radiation therapy and poorly executed radical surgery which were carried out in an attempt to relieve a papillomatosis of the larynx. His larynx has been kept open by core molds. Previously, there was a total laryngeal stenosis. The two laryngostomies left an opening in the neck of approximately two and one-half inches. This opening was closed to one of approximately one-half inch, through which most of his breathing is done. The laryngeal opening is a 16 French in size.

When this case was previously presented, the question was asked whether or not a plastic operation might be performed, possibly of a bridge implantation of cartilage, anteriorly. This procedure was not advised in the discussion that took place, mainly because of the great possibility of failure and the establishment of a possibly worse condition. Incidentally, this young man has a good pharyngeal voice. There is no movement whatsoever in the tissues of his larynx.

The second presentation is that of the little lad, Boby Sipple, who was presented twice before the Association, and whose condition was that of a congenital esophageal fistula that was closed by a plastic procedure transtracheally. [Trans. A. L. A. 1939, p. 147; Trans. A. L. A. 1940, p. 148.]

The boy's condition can be definitely reported as cured. He is now 10 years old, weighs 60 pounds and has grown approximately six inches since the last time he was presented. (In 1940 he weighed 40 pounds.) He takes part in all his school activities and is well up in his classes, both in regard to behavior and to studies.

This was a most interesting case because of the attempt that was made by a physician to dilate a cardiospasm. The child was given a long length of string to swallow, with the idea of passing the instrument down on the string as a guide. As pointed out by several members of this Association and by others, particularly Dr. Porter P. Vinson of Richmond, Va., a string should never be used where there is a possibility of a tracheo-esophageal fistula, because of the danger of the string winding itself around the tissues between the normal laryngeal opening and the fistulous opening. This occurred in this child and it was with difficulty that the foreign body, which was 10 yards and 26 inches in length, was removed by my former associate, Dr. David Jones, at the Manhattan Eye, Ear and Throat Hospital. However, at the time the string was swallowed, the diagnosis of tracheo-esophageal fistula had not been established.

Two operations on the fistula, approximately two months apart, resulted in permanent closure.

It is with pride that I recall your attention to this cured case.

The third case report is that of the seven-months-old child with marked dyspnea due to compression of the structures of the neck by hygroma cysticum coli [Trans. A. L. A. 1940, p. 51]. Reports from the attending physician are that the child is well and growing normally.

It would seem that the treatment of aspiration and injection with a mild sclerosing fluid is deserving of a trial in these conditions before surgery is attempted.

The fourth case report is that of the 72-year-old patient with the lymphoma of the larynx [Trans. A. L. A. 1941, p. 134], he has gained six pounds (now weighing 224 pounds), and for a patient of his years looks exceptionally well. There has been no recurrence of the growth and his voice is entirely normal.

This patient was operated on in October 1940, and about a year afterward there occurred an enlargement of a lymph node at the angle of the jaw. This rapidly increased in size so that it was approximately one and one-half inches in diameter. Carious teeth with apical abscesses were found and removed, and there was a prompt absorption of the intumescence.

Recent examination shows no further enlargement of any of the lymph nodes, and the patient reports that he is feeling in splendid condition.

The reasons for reporting this case were: the size of the growth, the method of removal (laryngofissure) and the result in so far as the voice, which is normal, and the present condition are concerned.

DISCUSSION

DR. THOMAS E. CARMODY: I would like to ask Dr. Imperatori to explain what he did to close the fistula between the trachea and the esophagus, because it was very cleverly done.

DR. FREDERICK A. FIGI: I would like to ask why Dr. Imperatori has not closed this stenosed larynx.

DR. SAMUEL IGLAUER: I would like to ask if the child with the tracheo-esophageal fissure was ever given barium or lipiodol to swallow.

DR. IMPERATORI: The first question was asked by Dr. Carmody. He wanted to know how the fistula was closed. An external incision was made into the trachea and the trachea was opened and retracted. The fistula could be seen and with a probe one could enter the esophagus. It was a slit in the tracheal wall in the space in which there are no rings.

The mucous membrane was separated and an incision was made around the fistula. Because it required two procedures, I felt at that time that, if we used a purse-string suture, we would get a puckering of the posterior tracheal wall and perhaps some difficulty of breathing. We might destroy to some degree the expansibility of the trachea on coughing, laughing, etc. Instead of making a purse-string suture, I put in a series of sutures, one in the esophageal wall, one in the muscular wall and one in the mucosal wall of the trachea.

That held for three days and the child then developed to a mild degree the same symptoms, so there was definite indication of the fact that there was a leak.

I waited six weeks, and they were a very long six weeks because I was very anxious to cure this case. Then on exposing the fistula again through the same procedure, I found that the fistula was only about two or three millimeters in diameter. It was then a very simple procedure to denude the tissues and put a purse-string suture around the fistula and tie it off. The child made an uneventful recovery.

In answer to the question which Dr. Iglauer asked as to whether the child had been given lipiodol and barium, I should imagine that barium had been given, because from the time he was a few months

old a diagnosis of fistula had been made. He had been operated upon for that and also for cardiospasm.

I know Dr. Louis Clerf saw some of the x-ray films. It was a definite cardiospasm. but none of this material ever went into this child's trachea, Dr. Iglauer, and that is the strange thing.

I know Dr. Clerf has another case just like this, with exactly these findings.

You can put barium into the esophagus in the attempt to make a roentgenogram of the esophagus. Apparently in these cases of congenital fistula, when the material gets to the fistula, it contracts and none of it gets through. It is only when the patient is in a lying position that there is a regurgitation and some of the material gets into the trachea and produces the syndrome of coughing, strangling, etc.

There was somebody else who asked a question about the stenosis. Well, the impression I received from the discussions when I previously presented this case was that the best thing to do was to keep on dilating the stricture and this was done.

DR. FIGI: How old is the patient?

DR. IMPERATORI: Twenty-two.

DR. FIGI: I should think there might be a cure by laying this open, putting in a skin graft, putting in the closure, and inserting an arched cartilage bar, if necessary.

DR. IMPERATORI: That was what I wanted to do and I was told under no circumstances to do this. As I had never had any experience with the implantation of a cartilage arch, I was not certain it would hold and for that reason I did not do it.

Penetrating Wound of the Neck With Unusual Complications and Sequelae

(Case Report)

HENRY B. ORTON, M.D.

NEWARK, N. J.

(This paper appeared in full in the December 1942 issue)

DISCUSSION

DR. C. L. JACKSON: Dr. Orton's case reminds me of a case I had in which there was a penetrating wound caused by shrapnel, a piece of which lodged in the left upper lobe of the lung.

This patient developed a carcinoma in the left upper lobe and just about two years ago a successful pneumonectomy was done. This was not exactly a parallel case.

DR. ORTON (closing): I omitted reading part of my paper. When the lobe was sent to the laboratory, our pathologist in sectioning it said he found a gland alongside the region the foreign body had penetrated that was definitely carcinomatous. Now, whether it was or not I do not know, but the lobe is out so it cannot do any further harm.

Technic of Tracheotomy With the Use of the Sulfonamides in the Prevention of Wound Infection

(Case Report)

GABRIEL TUCKER, M.D.,

PHILADELPHIA, PA.

A tracheotomy wound is a potentially infected wound because of the fact that it communicates directly with the interior of the trachea. In the great majority of cases the trachea contains infection where a tracheotomy is required.

The methods of entering the trachea are two in number. First, if the trachea is to be preserved, the first ring is removed by subperichondrial elevation and a cross incision is made in the trachea sufficient in length to accommodate the tracheotomy cannula. Second, a vertical incision is made through three tracheal rings in the midline, the second, third and fourth preferably; the wound should be of sufficient length to expose the region of the trachea selected for the opening and for the control of hemorrhage. The thyroid isthmus is cut if necessary. After the trachea is entered, the tracheotomy tube is inserted and plain gauze impregnated with one of the sulfonamides (preferably the aqueous solution of microcrystalline sulfathiazole) is packed around the tube. Plain gauze tape is wound around the tube and packed firmly against the trachea, pushing aside

the overlying tissues including the muscles of the front of the neck. The usual split gauze dressing is then applied and the tapes tied. This pack accomplishes two things: it prevents subcutaneous emphysema and the sulfonamide content prevents wound infection. The sulfonamide pack is used for the first few days and after that a smaller plain gauze pack. Finally no pack at all is required in the dressing of the wound.

The use of sulfonamide gauze in packing the wound has prevented infection, has prevented the development of subcutaneous emphysema, and has allowed the wound to heal with minimal cicatrization and scarring of the neck.

DISCUSSION

Dr. Ralph A. Fenton: We have been using this procedure for the past year and a half. At the Oregon Medical School an ordinary powder blower is being used which is much easier. We do not like sulfanilamide packed into the wound because it is too soluble. We like sulfathiazole, but very little of it. We have found that by using the ordinary powder blower it is possible to get this same protective effect of "buttering" the cells with something which the germs do not like to eat. The sulfonamides do not produce merely a bacteriostatic action, but an effect which really interferes with the attack, particularly of the staphylococci and streptococci, on these very vulnerable cells in the neck.

We have tried this on quite a number of tracheotomy cases in both children and adults. It is also in use at the Contagious Hospital where tracheotomies are done for cases of diphtheria. In all of these cases the perfectly insoluble sulfathiazole is found to work well.

Also when there is a lung complication, the powder can easily be blown in through the tube, but one must not use very much of it.

Dr. Charles J. Imperatori: I would just like to amplify what Dr. Fenton said, particularly about blowing sulfathiazole into a wound. If too much is used, it will accumulate and act like concrete as it will stay undissolved.

The term "buttering" which he used certainly seems a very good one, and I would suggest to Dr. Fenton that, unless he has a very fine powder blower, a very good method of using any powder is that proposed last year by Dr. Gill in which he takes an ordinary soda straw, cuts it in half, pushes it into the powder and with a little puff blows it in.

DR. THOMAS E. CARMODY: In doing plastic work with cartilage grafts, I have used sulfanilamide and also sulfathiazole locally, and closed the wound and had no trouble. I have also used them in mastoid and sinus operations, experiencing no particular trouble from their use. As far as I know, this form of treatment first was used by Furstenberg. I have been using it for about two years, but I have not used it in tracheotomy cases. I see no reason why it should not be so used.

The powder blower, which Dr. Fenton suggests, is good; and I think the modification which Dr. Gill suggests is good. In the absence of a powder blower, drinking straws or tubes can be used. Anyway, the blowing of a little sulfonamide powder into a wound is good herapy, but one must keep in mind that the sodium salt is irritating. If one gets too much into a wound, it will cake, as Dr. Imperatori suggests.

DR. TUCKER: There is one point which I wanted to make which does not seem to have been made; that is, if you pack tightly around the tube you prevent subcutaneous emphysema. By putting the pack in and by wrapping the tube down to the trachea, you carry the preventive medication down to the trachea and, as you remove the tube, the wound heals very nicely. There is no difficulty about getting it in place if you pack around the tube in the way I demonstrated, leaving the retractors in.

In fact, in a number of cases other types of gauze were used and there was always some infection, whereas this method controls the hemorrhage and allows the wound to heal. In addition to the preventive effect of the sulfonamides on the development of the organism, this pack also prevents subcutaneous emphysema. The infection is prevented from extending into the dense tissues of the wound.

There is another thing which might be of interest to you. This paper, a study on inhalation of microcrystals of sulfonamides, which we mentioned and which is to be published, concerns itself with a special preparation of the sulfonamides. The crystals are very small.

I cannot give you the exact technique of how these crystals are produced as I do not know it exactly, but the material is subjected to sound. It is done in one of the physiological laboratories.

An alkaline solution is treated and the material comes out as a neutral salt of sulfathiazole. This has been used in sprays. It is

white, looks very much like cream and stays in suspension in normal saline.

DR. GEORGE B. WOOD: Is that suspension now available?

DR. TUCKER: Smith, Kline and French make some which, I think, is only for experimental use.

The Veins of the Pharynx

O. V. BATSON, M.D.

PHILADELPHIA, PA.

There is an extensive submucous venous plexus in the posterior part of the mouth and in the pharynx. In addition to draining the tissues of the area, the vessels are grouped in several places into large venous networks. There is a ring-form plexus around the entrance to the larynx, which is continuous with the vessels of the tongue dorsum in front and with the heavier midline anterior pharyngeal plexus below. These vessels establish drainage connections with the superior laryngeal vein and continue into the esophageal veins. On the posterior wall the plexus has a well-marked superior border, but continues below with the veins of the esophagus. Other connections to the plexus are on the outside of the constrictor muscles.

These veins. no doubt, are the source of the small hemorrhages that from time to time worry patients and physicians. They may be involved in acute pharyngeal infections and the region might profitably be studied by the pathologist.

DISCUSSION

DR. JOHN F. BARNHILL: The time has come when the anatomist who teaches the ear, nose and throat doctors must be a good otolaryngologist. To have the ordinary anatomist who knows his anatomy as Dr. Batson says it was known up to 1871 teach us now does not get us anywhere. We need to correlate anatomical knowledge with our everyday practice. All over this country courses in anatomy are being given and, in some instances at any rate, general anatomists are teaching our otolaryngologists. I do not believe that this is a very wise practice.

There should be in every school teaching these postgraduate courses a man who stands at the forefront of otolaryngology and

who has the ability to use that special anatomical knowledge. Unless that is done, we are not going to make much progress.

For instance, for an anatomist to say that the external wall of the superior constrictor muscle is covered by a plexus of veins, does not mean anything specially to you or to me; but if somebody comes along who has had great experience with the affections of those veins and he tells the student why he needs to know about them, that is of value. The general anatomist does not know about the clinical application.

Dr. Iglauer, how is your course taught?

DR. SAMUEL IGLAUER: We employ two laryngologists to teach the anatomy. The general anatomist teaches the blood and nerve supply, but not the specific details.

DR. BARNHILL: For instance, if in these courses, the vagus nerve with its branches to the sympathetic is described, the student does not get much out of it; but if somebody who has had great experience in the function of the nerve tells him about its reflexes, then he wants to know more about it.

If there is anything at all in what I say, it is that we need to teach the otolaryngologist a new line of anatomy.

DR. IGLAUER: I would like to ask Dr. Batson why he had to tie off any veins. Was it probably to prevent the spread of the injecting fluid into some territory he was not investigating? I don't understand why he had to tie off a vein which, in itself, produces—so to speak—an artefact.

DR. GORDON BERRY: May I ask Dr. Batson whether the veins which he described are within easy reach of the local anesthetics which we employ in operative work about the tonsils. I should judge that they are posterior to the posterior and anterior pillars of the palate which we inject.

DR, HARRIS P. MOSHER: I heartily agree with what has just been said about the teaching of anatomy in our line. I have been interested only in applied anatomy and I feel that only somebody who knows the applied anatomy can do this teaching. That has been my practice as far as I have been able to carry it out.

DR. BATSON (closing): If I may just speak for a moment about this problem of teaching anatomy, I think there has been too much of a tendency to include facts in anatomy which point up the

erudition of a professor but which are not of any great significance at the moment.

I get out a letter now and then which I wrote a few years ago to someone starting the course. In this letter I suggested that his anatomy should be the anatomy of the best current clinical practice and that he should not try to anticipate what might be useful in 1952, but to leave that to the men in 1952 to find out. I think we can show all the points in theoretical anatomy that we wish to with the use of practical examples.

As to Dr. Iglauer's question of why it was necessary to ligate the superior laryngeal veins, I am not sure that it was, but let us see the relationship. I injected from the dorsum of the tongue. The outflow from there is by way of the superior laryngeal vein. That is the most ready outflow because that vessel is larger and the communications go on down into the anterior plexus. So by ligating the superior laryngeal vein I duplicated much the same thing that happens every time we hold the breath and strain. I increased the pressure in the superior laryngeal vein and then allowed the annulated plexus in the region to fill up. I think that is physiological. Elze depended on either forcing the specimen, or one in which the valve was not competent, so he injected backward through the laryngeal vein. In at least half of my injections I was following the normal course of the blood. I do not think that is abnormal.

As to the local anesthesia problem, I have injected here the veins of the posterior pillar and the veins of the tonsil, and it is quite possible, I believe, to inject directly into one of these vessels, although the vessels are, for the most part, of very fine capillaries. The lymphatics of the region, which duplicate the course although not the size of the veins, could also, by inference, be injected directly. As a matter of fact, I have some specimens covering this same area.

Use of X-rays in the Larynx

FREDERICK M. LAW, M.D.

NEW YORK, N. Y.

Conventional roentgenograms of the larynx are not entirely satisfactory. It is impossible to obtain antero-posterior views owing to the superimposition of the spine.

Most reliance must be placed on the fluoroscopic examination, which must be made during and without phonation and preferably in the presence of the laryngologist.

The newer technique of body sectional roentgenogram is the only method by which the subglottic extension of the lesion can be secured. This shows a cross section of the larynx at any predetermined depth and excludes the image of the spine.

It is made by a synchronous shift of the tube and film during exposure and the apparatus is so adjusted as to cause the rays to be focused at any desired depth. At this spot the rays are stationary, but objects above or below this depth are blurred by movements of the ray.

DISCUSSION

DR. RALPH A. FENTON: May I ask Dr. Law whether, in his judgment, it is possible to get anything approximating the results of tomography by putting a piece of film in an impermeable envelope down into the lower part of the pharynx and making the x-ray image on that film? I would like some comment on that.

DR. C. L. JACKSON: I have long felt that the use of the x-ray was of great help in the diagnosis of laryngeal disease; this was so even in the days when we only had the lateral film. As. Dr. Law has so well illustrated this morning, a great advance has been made in the development of tomography.

I have with me just one slide which I thought might be of interest. It shows a neurofibroma in the larynx of a young woman. This is very nicely shown by the planigraph, while the conventional lateral view shows nothing but the obscuring of the ventricle; that is, the loss of the ventricle shadow. By the planigraph the tumor is beautifully outlined in contrast to the normal cord and the ventricle and the band on the other side. Dr. Van Loon, a member of our staff, removed this tumor by laryngofissure.

DR. HARRIS P. MOSHER: A lateral plate should be taken in order to rule out any abnormality such as the one Dr. Law showed. The old-fashioned plate is perfectly competent to tell us what we are going to deal with.

DR. O. V. BATSON: When I first learned about ossification of the larynx it was from Dr. Iglauer and this is a so-called ossification of the cricoid Haversian system. While it can be called calcification,

I think if we want to be really precise, we should refer to it as a pathological process and call this normal ossification.

DR. SAMUEL IGLAUER: Dr. Law stated that fluoroscopic examination of the larynx in the antero-posterior position was more or less futile. I would like to ask him whether it is not possible to see a limitation of motion of one cord in the antero-posterior view by using the fluoroscope. The Philadelphia group, I believe, describes the possibility of visualizing paralysis or impaired motion of one cord in the antero-posterior postion.

DR. FRANK R. SPENCER: In F. C. Omerod's last book on "Tuberculosis of the Upper Respiratory Tract" [F. C. Omerod, M.D., Bale Medical Publishers Ltd., London, 1939], there are a good many laminagraphs which are helpful in the diagnosis and differential diagnosis of tuberculosis. They are very well made and bear out much of the information which Dr. Law has given us here today for the diagnosis of laryngeal lesions.

In the past the x-ray has not been of a great value in the diagnosis of tuberculous lesions of the upper respiratory tract because we can usually see these by direct and indirect methods.

DR. CHARLES J. IMPERATORI: Dr. Law points out very definitely that there should be a lateral plate and a comparison made between it and the tomograph. Certainly the ventricles can be seen in the lateral plate, but you can evaluate them much better because you have two ventricles which are exactly the same size when you are examining the tomograph. Also the most important consideration of the tomograph is that you get a very good view of and you are able to evaluate the condition of the subglottic area.

From a clinical standpoint that is of very great importance because normally even with the direct examination, unless the mass is large, you cannot evaluate it so well. So I feel this method of procedure in conjunction with the older method of the lateral exposure is of great value.

My attention was originally directed to this by Dr. Law long before we knew anything about tomographs or laminagraphs. He had used this method in the location of foreign bodies during the last war in France. And several years ago, when Dr. Felix E. Leborgne of Montevideo was here in the United States and showed quite a number of these photographs and really rejuvenated the thing from the standpoint of the laryngologist, we felt we had another thing to add to our armamentarium to make a proper diagnosis.

DR. LAW (closing): The method of viewing the larynx by means of a film inserted into the hypopharynx was employed many years ago. That was before the days of the planigraph and it did give us a very good view, but if any of you were present when the film was put into the hypopharynx, I don't think you would want to try it on yourself. I was very enthusiastic when I first heard of it and immediately tried it. Well, we had quite a mess, but when the planigraph came out and was first demonstrated spectacularly by Dr. Felix E. Leborgne of Montevideo I built my own, as there was none on the market. It did not cost much but gives very satisfactory results.

As far as the fluoroscopic examination in the antero-posterior view is concerned, there may be times when you can visualize a cord. We all do not have the same eye, and some people can see much more than others on the fluoroscope. Probably Dr. Jackson can say what Dr. Chamberlain thinks about this. The view with the planigraph is so satisfactory you just waste your time in a risky fluoroscopic examination. It is risky to yourself and to your patient.

X-ray Treatment of Diseases of the Larynx

MAURICE LENZ, M.D.

NEW YORK, N. Y.

(This paper appears in full on page 85)

DISCUSSION

DR. JOHN H. FOSTER: I do not make any pretense of having any deep knowledge of roentgen therapy. Whatever opinions I have formed in regard to it have been those of a clinician and from observing patients who have been treated.

I am not going to say very much about cancer of the larynx except that with my experience I would subject any patient with undifferentiated cancer of the larynx to it, except the case in which the cartilage was affected or if I thought x-ray therapy would cause a breaking down of the cartilage. Therefore, the cartilage should be first removed and the larynx then x-rayed.

Of course, the borderline cases between differentiated and undifferentiated carcinoma present the opportunity for a considerable difference of opinion.

The only point I wanted to particularly raise is in regard to a subject in which I have been very much interested for the last twelve years; that is, x-ray therapy in papillomatosis of the larynx in children. I have yet to see a case of papillomatosis in a child, that has not been subjected to operation, that has not cleared up under x-ray therapy if I have been able to get the roentgenologist to apply the dosage I think is indicated in these cases.

The question lies in the essential nature of papillomata. I do not think they are neoplasms in the ordinary sense of the word, but are growths which result from some systemic condition.

I think the dosage to be used in papillomatosis should be small, one that causes the papillomata to become absorbed. I think the failure to get the results I have been able to get has been due to the fact that the roentgenologists will not use that sort of dosage. They all seem to feel they must use a dose that will destroy these growths, a dose which I do not believe is indicated at all.

I know in my town I have only one roentgenologist whom I can depend on to use the dosage I advocate. These men usually take the attitude that I don't know anything about x-ray therapy, and I am perfectly willing to admit it; but if one turns a case over to the average x-ray man and tells him what kind of treatment is to be given, one will discover that he uses the dosage of the Coutard treatment because he feels that with the small dosage at weekly intervals there will be a recurrence.

The first patient I reported on in 1930 came back to me in ten years with a single papilloma of the vocal cord, which I removed. One other patient returned with one large papilloma at the site of a tracheotomy wound. In none of these cases has there been a recurrence of the general papillomatosis which was present at the time of my first general treatment. These patients have perfectly normal larynges after the papillomata are absorbed and one cannot tell that there has ever been anything the matter with them.

Dr. John F. Barnhill: The essayist has touched on a point which has interested me for many years. The point is: why is malignancy of the arytenoid often fatal and that of the cord itself not so? For a number of years I have tried to satisfy myself why this is so. My final conclusion is that it is entirely a question of the lymphatics.

Doubtless some of you have seen an illustration, which I have seen in one or two different books, showing the distribution of the capillary lymphatic trunks and their union inside the larynx. If you

remember that picture, you will remember also that there is scarcely any lymph channel on the cord itself. Many who have investigated the subject say that there are none on the cords and they never find them; but if one investigates the arytenoids and the region above and below the arytenoids, in other words, the region where extrinsic cancer develops, one will find the densest kind of distribution of lymph vessels. Therefore, I think, it is a question of lymph distribution. I would like to hear what the essayist has to say about this.

DR. MERVIN C. MYERSON: Dr. Lenz has given us a conservative, lucid, praiseworthy and modest presentation. I would like to touch upon several unrelated points in this subject.

In the matter of tuberculosis of the larynx, I doubt whether American laryngologists will ever subject their patients to x-ray therapy. This is because there is getting to be a more universal and widespread understanding of the fact that it is only those larynges which have the ability to produce fibrous tissue in which we can expect healing. Therefore, any form of therapy we apply to this disease will give us results if we are treating this particular type of disease in the larynx. When we are treating the ulcerating, disintegrating type of lesion, nothing will help and it is safe to say that the chronic, productive type of disease in the tuberculous larynx will heal without any laryngeal treatment. It might heal a little faster if one applies the cautery and certain stimulating medicaments.

In the matter of carcinoma of the larynx, the big consideration which occurs to me is the matter of the cartilages and the injury they are subjected to from x-ray.

There seems to be considerable difference of opinion among laryngologists who are interested in the surgery of the cancerous larynx as to whether or not an irradiated patient should be operated upon. Many will not operate on patients who have had x-ray therapy. I have come to feel that these patients with telangiectatic and stiff subcutaneous tissues can be operated on with some expectation of good results.

I would like to ask Dr. Lenz whether it is possible for the x-ray therapist to carry out a technique in his treatment of these cases which would leave an unexposed area in the midline of the neck, so that, if future surgery is necessary or decided upon, the vitality of the tissues through which the surgeon cuts will not be too greatly compromised.

I would also like to pose a question: Are we not, as laryngeal surgeons, cleaving too closely to the indications for surgery of the larynx that were laid down thirty or more years ago? Might it not now be proper to revise our attitude on the management of cancer of the larynx that is not entirely intrinsic?

Last week, at a local medical society meeting, I reported two cases which I operated upon, which ordinarily would not have been subjected to surgery and would certainly not have responded favorably to x-ray therapy. They were both undifferentiated squamous cell carcinomata.

The first case was a man who had an enlarged mass of glands on the left side of the neck and had a bilateral superglottic extension of his cancer. I removed the gland and a week later removed the larynx. The man survived for three and one-half years and died of a metastatic lesion in the lung. Now I think that, if one can give a man a comfortable existence for three and one-half years, surgery in such a case is well advised.

In the other case, a cancer must have originated in the epiglottis and extended to the larynx. It covered his larynx so that nothing could be seen but an enormous fungating mass. It had also extended into the base of the tongue. I removed this mass through a pharyngotomy. The man is still alive thirteen or fourteen months after the operation. He received a full course of x-ray therapy, and the skin was not too badly compromised when he came back. I removed the larynx last week and encountered an abscess which I did not anticipate. I hope his tissues will heal.

DR. H. B. ORTON: About four or five years ago at the Academy of Medicine in New York, when I was on the program with Dr. Lenz, I stated that I had yet to see a case of carcinoma of the larynx cured by radiation. Apparently, at that time, I was right, but now I make public the statement that I have seen such cases cured by Dr. Lenz. I think Dr. Lenz has given us one of the most honest reports of x-ray therapy of the larynx that I have heard. I will confine all my remarks to carcinoma of the larynx.

I will operate on the larynx whenever surgery is possible. In the intrinsic type, which Dr. Lenz wishes to treat by x-ray and in which the growth is at the junction of the anterior and middle third of the cord, I still think surgery is the choice.

In the so-called extrinsic tyes, those involving the epiglottis, the aryepiglottic folds and the arytenoids, if the patient is in good

physical condition, if there are not too many glands and if they are freely movable, I still prefer to do radical surgery and then supplement it with x-ray therapy.

Dr. Lenz stated that in one of his cases a carcinoma was cut across. I would like to ask him if it was high up in the epiglottic region or at the anterior commissure region because that might bring into question the space of Boyer. If a carcinoma penetrates the anterior commissure, one will cut through it, and for that reason in every laryngectomy which I do the hyoid bone is removed with the larynx.

Dr. Frederick A. Figi: This is the most frank statement on the subject that I have ever heard from a radiologist.

Our experience in the treatment of blastomycosis and rhinoscleroma with x-ray corresponds with that of Dr. Lenz.

With regard to the treatment of papillomata, we use irradiation somewhat, but we are not as convinced of its efficacy as Dr. Foster is. As a matter of fact, I have seen several cases of papillomata in children in which malignant changes developed after irradiation, even at the age of five or six. Whether these changes would have occurred had not irradiation therapy been given is, of course, open to question. But it was our feeling that the irradiation was a definite factor in the development of the malignant change.

It is still our feeling that any laryngeal carcinoma which is operable should be dealt with surgically. One can do a much more radical removal through a laryngofissure than some of the older writers on the subject would have us believe. As a matter of fact, some patients, even with quite extensive laryngeal carcinomas, subjected to laryngofissure, do remarkably well.

Dr. Jackson may recall a patient on whom I happened to be operating when he visited us five or six years ago—a man with a fixed carcinoma of one side of the larynx, a grade 2 lesion. I had advised laryngectomy and was firmly convinced, even after exploring the growth through a tube, that a laryngectomy should be done. However, the patient would not tolerate a laryngectomy, so we electrocoagulated the growth very thoroughly and removed the involved cartilage. That patient is still perfectly well.

The question which Dr. Myerson brings up, as to whether a patient whose laryngeal carcinoma has been irradiated should be later subjected to radical surgery is of interest. In many such cases healing

takes place almost as well as in a case that has not had intensive irradiation, and we have seen a number of them that have remained well during a period of some years.

The matter of radiation therapy for carcinoma of the larynx cannot be dismissed too lightly in favor of surgery. One cannot help but develop a certain amount of enthusiasm when he sees cases which are frankly inoperable, with metastatic nodes present in the neck, go along after fractional dosage of roentgen rays without evidence of recurrence for a matter of several years. How much longer they will remain free from malignancy is, of course, questionable. But a number of these patients had obviously only a few months to live at the time they were sent for radiation.

Attempting to answer this question regarding the reasons why lesions which involve the arytenoids are less responsive to irradiation than those involving the epiglottis, I am wondering whether it is not due to a difference in the activity of the growth. Ordinarily, lesions originating on the epiglottis are of a low degree of malignancy and metastasize very late, while those originating on the arytenoid are, with few exceptions, highly malignant and metastasize very actively.

Dr. John D. Kernan: I have seen Dr. Lenz' work almost since its inception, and the thing that I have been struck by is the great improvement which has occurred in the application of roentgen therapy to diseases of the larynx. Of course, I can remember when cancer was cured by x-ray and the whole larynx would slough out. I can recall one or two cases of that kind.

I can recall several patients which Dr. Lenz has recently treated for me which he did not mention because they are not five-year cures, but they have been well for two or three years. In those patients, not only did the carcinoma disappear, but it disappeared without a trace either inside or outside the larynx. There is no telangiectasis or scar tissue in the skin. They have perfect vocal cords with a perfect voice, so that you may say that early carcinomata of the larynx, those limited to the cord and with a mobile cord, are cured as he treats them.

Laryngectomy is not a cure for a carcinoma of the larynx. It is analogous to amputating the foot caught in the trap, but when you see a carcinoma disappear without trace, that is a cure. So it may actually be said that Dr. Lenz cures cancers of the larynx.

Dr. Samuel Salinger: If Dr. Lenz reflects the generally accepted views among radiotherapists on this point, I would say that a

great change has taken place in their attitude, because he admits that the histology of the tumor is no longer any criterion for the employment of radiotherapy. He admits that infiltration and fixation are contraindications to x-ray therapy, and he has shown his best results in the one type of case in which surgery has been so eminently successful; namely, the isolated lesion with the movable cord. The question then arises whether in choosing radiotherapy instead of surgery with its known background and record one is willing to subject the patient to six or seven weeks of discomfort and pain in order to achieve the results which he has shown us here.

I still feel that, when there is a difference of opinion or when there is a disinclination on the part of the patient to subject himself to surgery and he submits to irradiation, there must be a time during the course of the radiation therapy when it should either be interrupted or completed; interrupted for the purpose of resorting to surgery, because I still feel that after complete irradiation has been given there is some risk in surgery.

Dr. Lenz admits that the margin of safety between the point at which the tissues have received their maximum safe dosage and the point at which damage can be done is very small. In cases in which the patient insists on irradiation, it has been my practice to interrupt the irradiation and insist on surgery if I determine that no further progress is being made by the irradiation.

My experience with postoperative irradiation has been very good, and I agree with Dr. Lenz that it can be given with safety and that the results are very good.

Dr. T. E. Walsh: May I ask Dr. Lenz a question regarding the total dosage he employs in cases which are irradiated following laryngectomy.

We have recently seen a patient on whom a laryngectomy was done about a year ago. This was followed by irradiation therapy. The patient has a recurrence in the pharyngostomy opening. I am wondering how much more irradiation can be given safely, whether it can be given at all following his original irradiation, and whether a time factor should be allowed between the first dose of radiation and any subsequent dosage.

Dr. Thomas C. Galloway: In Coutard's report, which is probably best in an extensive series, 27 per cent were reported cured for five years. Subsequently, however, about one-third of these had recurrences.

I would like to ask Dr. Lenz what limits he would fix for the time after which one may assume a definite cure, following radiotherapy, has taken place.

DR. CHARLES J. IMPERATORI: I simply want to report briefly on two of Dr. Lenz's patients with which I had something to do, the patient with the rhinoscleroma and the one I did the laryngectomy on after the radiation therapy. Those patients remained well.

I want to ask Dr. Lenz if he has come to any definite conclusions about the indications for radiation therapy? This is a hard question. Which cases should be irradiated and which should receive surgical treatment? I do not mean advanced cases which require a laryngectomy nor the cases which are evidently beginning to invade a little bit beyond the area of the growth on the cord. I am speaking about the early cases which we see and I feel very definitely that the proper treatment for those patients is surgery.

I would also like to ask Dr. Lenz if he has had any experience with the role that water plays in irradiation of the tissues? Recently there has been a book published on fluorescent materials. There is a reaction which takes place in certain fluorescent materials when they are injected into the tissues and the tissues irradiated. The ultraviolet ray apparently is activated in such a way that nuclei are destroyed. These experiments which have been conducted by Dr. Jacques LeMent are described in a book which he has recently written on "Fluorescent Chemicals and their Application" (Chemical Book Publishing Co., Brooklyn, N. Y.).

It seems to be an entirely new principle of therapeutic approach and I should think that its being on the topic of x-ray and radiation, Dr. Lenz might be able to enlighten us about it and tell us whether or not this is a proper therapeutic procedure and one which might help.

The use of "heavy" water has been suggested in some of these cases but purely from an experimental standpoint. Whether or not there have been any cures with the injection of "heavy" water into the tissues which have then been irradiated, I do not know.

DR. LENZ (closing): Dr. Foster brought out his experience with low voltage x-ray therapy, and he has published a number of articles on it which prove his point. However, I think the answer to treatment of papillomata in children was brought out by Dr. Broyles. It seems to me that estrogen therapy is probably simpler and better. However, as an x-ray man, naturally I see no reason why x-ray ther-

apy should not be used if the laryngologists insist upon this form of treatment.

Dr. Barnhill was good enough to bring out a point about the lymphatics of the arytenoid. I wonder how one can correlate the extension to the lymph nodes with this point. These patients die with severe local infection. One sees so many of them with a necrotic wound, and it seems to me that the cartilage necrosis, along with the long standing chronic infection, is sufficient to explain their deaths. But there is no question about the point, which somebody else brought out, that these arytenoid cases have many more metastases.

I am sure Dr. Barnhill knows so very much more about the anatomy of the laryngeal lymphatics that I cannot comment on that question intelligently.

In discussing the lack of indication for x-ray therapy, Dr. Myerson brought out the fact of the natural tendency of laryngeal tuberculosis to heal. In general I agree with him, but Rickman's work [A. Backmeister und L. Rickman, Die Roentgen behandlung der Lungen u. Kehlkopf Tuberkulose, George Thieme, Leipzig, 1924] cannot be lightly dismissed. Rickman is in charge of a sanatorium and is not a radiologist. He reports two large series; in one all the sanatorium care had been given plus x-ray therapy, while the other series received the sanatorium treatment without the x-ray therapy. He claims that the results in the first series were better.

As I said, I do no believe that x-ray therapy should be carried out except in a tuberculosis sanatorium or hospital.

Dr. Myerson also asked the question: "Can we irradiate so as to leave a midline space where it would be safe to operate?" I think we do this ordinarily, because we are afraid of overlapping action and getting a burn in the midline; so I think it is safe to operate on these cases after irradiation.

Again I have no quarrel either with him, Dr. Orton, or anyone else who has successfully operated on extrinsic types. Every once in a while I am sure it can be done, but I wonder in, say, 100 extrinsic types how many patients remain well for ten years. That is the only criterion as to whether one should operate or irradiate.

In talking about necrosis of the cartilage, I think it is unfair to attribute every necrosis of the cartilage following x-ray treatment to that treatment, unless one can show microscopically that the cartilage was not invaded by cancer cells.

Now we come to a difficult question: which of the early cases should be subjected to surgery and which should be treated by roentgen therapy? I do not know. I have not enough experience. I have only a few cases. I can only say that of those which I have treated, the majority have remained well. I think this is a question for individual decision. Our usual procedure is to tell the patient: "If you are going to have a laryngofissure, you are going to be through with all your treatment in a week. If you are going to have x-ray therapy it is going to take at least a month and you will have several weeks of discomfort. The voice in the end will be better." I think that is fair. Then the patient decides. Recently, one of the surgeons at the Presbyterian Hospital and I saw a patient jointly and put the decision up to him. The surgeon pressed his point a little stronger and operated on the patient. In this particular case there was a very peculiar complication in that the patient developed a very severe subcutaneous emphysema of most of the body. That is a very rare complication, but neither the surgeon nor the patient nor I expected it.

Dr. Imperatori brought out the point about "heavy" water. All types of heavy elements have been tried in combination with x-ray therapy. The difficulty with all of these methods is this: These elements do not select the cancer cell exclusively but react just as heavily on the normal cells and, therefore, there is no advantage in this form of treatment. For instance, when colloidal lead was used to treat cancer, just as much colloidal lead was deposited in the bone marrow as in the cancer and the result was that these patients died in spite of numerous transfusions. They all died of anemia. Local injections of heavy water within the area of the larynx will deposit just as much in the normal cells as in the cancer cells and therefore it does not seem to me an advantageous form of treatment.

I have known of Dr. Orton's views, and no one respects his beautiful surgery more than I do. It is a revelation to me to have him say that he is satisfied that we do cure some of the cases.

Again I have no quarrel with anyone who wants to treat the early cases by laryngofissure and cordectomy, as Dr. Orton or Dr. Figi would do. I just offer this suggestion, that, if for any reason the laryngologist or the patient decides against surgery, x-ray therapy really does give him a chance in an early lesion.

Irradiation of cells produces maturation; that is, the cells become more mature and more differentiated; therefore, I doubt whether the case which Dr. Figi cited in which a carcinoma developed

in a child after x-ray therapy could be attributed to the irradiation, but then again that is a moot point.

Occasionally we do as Dr. Salinger suggests. When after a few weeks' treatment, there is no regression of the tumor we ask the laryngologist to operate on the case. We have done that on several occasions.

Dr. Walsh wanted to know whether a patient who has had a full treatment can get another treatment. The experience which I have had has been this: When we administer with 200,000 volts, with a one to two mm. filter of copper, a daily dose of not more than 125 to 150 R to each of the laryngeal fields and a total dose of around 3,000 R to each of the laryngeal fields, provided that the fields are not larger than 6 x 8 cms., we have repeated that dose two and three years later.

In one case we repeated a dose, I think, in six or seven months. The cancer was not cured, but the tissues remained healthy.

I might say here also that in the recurrences in the tracheotomy wound which one occasionally sees after laryngectomy, we have not been successful in arresting the disease.

Dr. Orton asked where the extension was in those cases in which the cancer had been cut across. I remember that two of them had penetrated through the thyroid cartilage.

Dr. Galloway asked the question, when is cancer cured after irradiation. When is cancer cured after laryngectomy? I think the answer is the same to both questions. I don't know when it is cured. I should say that an arbitrary figure of five years, which the surgeons use, is fair.

Chondroma of the Larynx

E. Trible Gatewood, M.D.

Richmond, Va.

This lesion was first described by Huesinger in 1822. Since this time only 83 cases have been recorded in the literature. Whether this fact is due to the rarity of the disease or to the infrequency in which it is detected is debatable.

Because the lesion is more often situated on the inner cricoid plate, independent of the vocal cords, it may exist for years with or

without atypical periodic symptoms. In other instances the first indication of the disease may be dramatic dyspnea. When this occurs, spasm or inflammatory change is associated with it.

Routine mirror examination will frequently miss this lesion. Roentgen examination is indispensable. Biopsies are frequently difficult to obtain because of the firm consistency. The disease is benign and nonrecurring. Patients with this disease may easily receive misdirected treatments for years. The dyspnea may simulate asthma.

It would seem from a review of the literature that a large percentage of cases of chondroma of the larynx are not encountered by the laryngologist until an emergency tracheotomy is needed or until the growth has advanced to a stage whereby total laryngectomy is required. Laryngofissure is the operation of choice where there is a possible chance of physiologic restoration.

DISCUSSION

Dr. E. D. King: I would like to ask Dr. Gatewood a question. In his case reports he referred to one in which the young man developed sudden dyspnea. Was that a chondroma?

Dr. Gatewood: Dr. Jackson had a case like that six or eight years ago which was not reported. That was a tracheal tumor because the site was in the region of the first ring of the trachea rather than in the cricoid region.

Anterior Commissure Tendon

E. N. Broyles, M.D.

Baltimore, Md.

Serial cross sections of the anterior commissure region of a normal larynx demonstrates the firm attachment of the vocal cords into the midline of the thyroid cartilage by means of the anterior commissure tendon. The internal perichondrium is not firmly attached laterally, but in the midline the tendon blends into cartilage with no plane of cleavage.

In the lower portion of the thyroid cartilage there is no firm attachment; the tendon sweeps around and does not enter the cartilage.

It is suggested that this crista of the thyroid cartilage be removed along with the diseased cord in cases of carcinoma of the anterior commissure region.

DISCUSSION

DR. H. B. ORTON: I was very much interested to see this, Dr. Broyles, because it is what I have been talking about for a number of years. If any growth involves that area, I would do a total laryngectomy. It is from the area that Dr. Broyles speaks of that growth penetrates the cartilage and enters the space of Boyer.

DR. C. L. JACKSON: I found this presentation of Dr. Broyles most instructive and illuminating, and it has certainly inspired me to have even more respect for the lesions at the anterior commissure than I had before. But I do not think—and I would like to have Dr. Broyles evaluate his feeling on this point—that it absolutely disqualifies the anterior commissure type of laryngofissure operation in which we go through the cartilage from the outside and then separate off the lesion with the adjacent tissue on each side before making the excision of the tumor. I think the statistics prove that that operation has justified itself in the cases of anterior commissure lesions.

It is true that statistics show that laryngofissure in these cases is not attended with as high a percentage of cures as in a lesion involving the middle third of the cord. However, I still believe there are cases of small lesions of the anterior commissure which justify the laryngofissure.

DR. BROYLES (closing): The point I wanted to bring out mostly was the fact—and I know of Dr. Jackson's success with the anterior commissure operative procedure—that the perichondrium does not extend completely around the angle of the thyroid, and when you cut through the cartilage anteriorly you must make a very careful examination of your specimen, especially of the anterior portion, to be sure you have not left a little carcinoma in that region.

CHICAGO LARYNGOLOGICAL AND OTOLOGICAL SOCIETY

Meeting of April 6, 1942

THE PRESIDENT, DR. JEROME F. STRAUSS, IN THE CHAIR

The Developmental Anatomy of the Human Stapes

BARRY J. ANSON, M.D.

AND

EARL W. CAULDWELL, PH.D.

(This paper appears in full in the December issue)

DISCUSSION

DR. HENRY B. PERLMAN: Having had occasion recently to make a reconstruction of a portion of the labyrinth from serial sections, I can appreciate the great amount of work and careful judgment that has gone into the study that Dr. Anson has just presented. Perhaps the clinician assimilates this embryonal information in a different way from that of the anatomist, but somewhere in the background of both is the realization that there are gaps in our knowledge which must be filled in. As otologists we are continually confronted with the unanswered problems of the normal function of the stapes and the whole baffling problem of otosclerosis with stapedial fixation. In these embryonal investigations of Professor Anson on the development of the stapes and the adjacent otic capsule, as in the studies of Professor Bast on the growth and the ossification of the otic capsule, we look for clues to the solution of some of these problems. The embryonic development of the ear is such a complex process that it is amazing that nature does not often become confused and produce an imperfect mechanism. But embryonic malformations of the ear are rarely encountered either in the clinic or in the laboratory. We have just learned that the stapes is full grown in the five-month-old fetus, and in general the conducting mechanism and the labyrinth with its intimate bony capsule is full grown at birth. From that time

on, since no growth is required, the capsule bone remains as inert as any living tissue can be. The periosteal layer of the capsule is an exception. With its growth the oval window niche may become very deep, so that it surrounds almost the entire stapes. The crura then are very close to the wall of the niche. Under these circumstances bands of adhesions are easily formed between the crura and the niche wall and may impair the motion of the stapes. The niche is so deep and narrow that it is readily obliterated by connective tissue in chronic inflammation and in the radical mastoid cavity.

Such an ear, even without an ossicular chain, functions less effectively to air-borne sound than one in which the niche is open and the stapes is not bound by connective tissue. In endemic cretinism Nager has shown that the overgrowth of the periosteal layer of the otic capsule on the middle ear side may be so great as to obliterate the oval and round window niche.

We are born with full-grown, mature labyrinths. The enchondral and endosteal layers of the labyrinth capsule remain inactive the rest of our lives. When we look at a focus of otosclerosis under the microscope, we see that it is made up of new bone which is replacing the old bone of the capsule. Where does this new bone arise from when all this normal capsule bone is so inert? There is one island of connective tissue and cartilage in the capsule that probably is a clue to this question. That is the fissula ante fenestrum. It is interesting that this structure is found only in the human ear. As we have seen, the structure extends through the entire bony capsule, just in front of the oval window. We do not know why it is there, but any stimulus inducing bone activity can find in this unstable tissue a suitable medium to react, and this stimulus may start here a process of new bone formation at the expense of the old capsule bone. The process may stop before the annular ligament is invaded and then no clinical symptoms are produced. Otosclerosis most commonly begins in this part of the otic capsule. Other minute foci of unstable preosseous and osseous tissue may, as Bast has suggested, be present in some otic capsules and may be responsible for foci of otosclerosis found in other regions than that near the oval window. In embryonal studies such as that reported here, we seek to establish a normal pattern of this development of the otic capsule and the stapes. This may help us subsequently to find abnormal patterns, as, perhaps, in the fetus of a mother having otosclerosis.

The stapes weighs 2.8 mg. This small mass moves through an exceedingly small distance when driven by the rest of the conducting mechanism in response to an acoustic impulse. While for thresh-

old sounds the amplitude of movement is much less than the diameter of a molecule of water in a connective tissue fiber of the annular ligament, much greater movements are imparted to it by large acoustic stimuli. These movements are great enough to be visualized with small magnification, and can be photographed. The movements of the footplate are not simple in-and-out, piston-like displacements but a rocking motion, greatest at the anterior end of the footplate. This is facilitated by the increased width of the annular ligament in the anterior portion. At the same time the elasticity of the annular ligament is great enough to permit mass and slow displacement of the entire stapes as when we apply static pressure on the drum which we often do with a Seigle's speculum, or when the stapedius muscle pulls the unattached stapes into the oval window niche.

DR. BARRY J. ANSON (closing): We are attempting in this anatomic study of the human stapes to establish the norm in gross form and in histologic structure. Without such knowledge of stapedial morphology, based upon the developmental history of the ossicle, it would not be possible to judge accurately the extent and kind of damage produced by otosclerosis, otitis and kindred diseases. We have under way a comparable study of the malleus and the incus.

It is recognized that the cartilage of the vestibular (oval) window and the various tissues surrounding and occupying the fissula ante fenestrum are inseparably linked with the stapes in pathologic change. These portions of the capsule have been studied extensively in our laboratory; I have purposely omitted mention of them because even a brief report upon the results of our investigations would have lengthened my paper beyond reasonable bounds.

Prosthetic Correction of Inoperable Facial Defects

ADOLPH M. BROWN, M.D.

(Abstract)

The patient, a man in his twenties, has been under treatment at three university clinics during the past eight years. He has a 4+ Wassermann and Kahn reaction. Dr. Tibor Benedek raised two cantharides blisters on his skin, aspirated the serum from the blisters and injected the liquid into four guinea pigs. All the animals suffered total destruction of the face, including the eyes. Benedek found Leishmann bodies in the livers of all four animals.

At present the patient is getting fuadin injections and says that he feels pain in the lesions on the face after each injection. He himself feels that the antimony injections are controlling the lesions. He has no lips, therefore salivation has been a problem. Dr. T. K. Lawless feels that much of the skin destruction is caused by salivation.

Since the prosthetic mask has been furnished him, he has improved mentally, is well oriented, well balanced, and quite intelligent. The mask is held in place by an adhesive made of gum mastic, resin and chloroform. It is waterproof, perspiration proof, and thus far has been found to be nonallergic. One patient was found to be sensitive to the latex rubber. This mask has been provided with recesses inside the prosthesis which contain cotton pads to collect the saliva and by which we hope to control skin destruction.

DISCUSSION

Dr. Francis Lederer: This excellent work should not be passed without commendation. Certainly great appreciation is voiced by the patient, whose personality and outlook on life have been helped tremendously. The history is interesting; it was reported as the first autochthonous case of leishmaniasis by Benedek (J. Trop. Medicine and Hygiene, 43, June 1, 1940). No source of infection was discovered in this case. It was Benedek's contention that American leishmaniasis was confused with syphilis and other infectious granulomas. When I first observed this patient I was reminded of cases of syphilis mutilans. He is a congenital syphilitic, but the histologic and bacteriologic studies disclosed Leishman bodies.

The subject of rubber prostheses has long interested me, for I presented a paper on the use of such material before this Society in 1928 [Arch. Otolaryng. 8:531 (Nov.), 1928]. At that time we were employing a gelatin mixture and later Dr. Peluse in my department reported the use of latex rubber. Obtaining the proper color is the great problem. The indications for the use of such material are quite clear. It can be used in cases where extensive destruction does not warrant plastic repair, and in replacing parts, such as the ear or nose, where further observation of the area is desirable before attempting reparative surgery. This work is a labor of love, and when we have men in our midst who possess the requisite artistic talent and who will sacrifice the time necessary, they are to be congratulated. We must consider ourselves fortunate in having their aid.

Dr. Elmer Hagens: How durable are the masks and how long does one last?

DR. ALFRED LEWY: I would suggest using radiation instead of medication to reduce the salivary secretion. It is commonly used for that purpose.

DR. ADOLPH M. BROWN (closing): This patient has had three masks since October. The first one wore out quickly because he had not learned how to handle it. He is now quite expert and removes and replaces the prosthesis with skill, as you have seen. Since the jaw is ankylosed, he removes the prosthesis a few times each day in order to eat. However, he is able to take liquids through a straw or drinking tube through the artificial lips of the mask. A latex prosthesis should last several months. This prosthesis is exceptionally large—in fact there is no record in the literature of one as large as this. The smaller prostheses last much longer.

A New Approach to the Treatment of Snoring

JEROME F. STRAUSS, M.D.

(Abstract)

On the basis of the theory that true functional snoring is caused by the vibrations of the soft palate, the uvula and the posterior pillars and that the sound produced is related to the natural periodic vibration of the tissues involved, it is suggested that the "fluttering" factors be modified by producing a controlled fibrosis in the vibrating soft tissues by the injection of sclerosing solutions such as sodium psylliate.

In this very preliminary report four cases are presented, in one of which snoring has been eliminated, two show definite improvement, and one shows no result whatsoever.

DISCUSSION

DR. SAMUEL SALINGER: Dr. Strauss deserves a tremendous lot of credit for undertaking serious study of a topic so grossly neglected. The fact that he could find only two references in the literature shows that the subject has been woefully shunned. Knowing nothing of the scientific aspect of the subject, I naturally thought of its humorous aspect and looked it up in Bartlett's quotations, only to find one from Steinbeck and one from Shakespeare, neither of them very funny.

I always had the idea that snoring was due to lack of tonicity in the soft palate which came on during sleep and depended not only on anatomic configuration but also on the degree of relaxation or depth of sleep. People have good nights and bad nights, and it seemed to me that the depth of sleep was the probable solution of the thing. Dr. Strauss has suggested something else that rather struck home, namely, the question of the flutter rate of the soft palate. His theory is that he can change that flutter rate by altering the density of the soft palate in the patient and thus eliminate snoring. It just occurred to me that no one has thought of investigating the question of snoring among patients who have had a tonsillectomy, particularly adults in whom scarring has taken place or with fusion of the pillars, stretching the palate and thus altering its shape and form. Perhaps a study of these patients postoperatively as well as preoperatively might throw some light on the subject. I think the unwilling victims of the snorer need help and any effort to solve the problem is most praiseworthy.

Dr. Howard C. Ballenger: Snoring in a child usually means an enlarged adenoid. However, in adults, I am impressed by the number who have an excessively high-arched hard palate, the so-called "Gothic arch palate." These people are frequently chronic snorers, even though their nasal passages are open and their palatine musculature seems normal.

Dr. Francis Lederer: The factor of nasal obstruction in the causation of snoring does not impress me very much. While patients have been referred for submucous resections because of snoring, I have never seen any good results from the operation.

Dr. Strauss did not mention the role of the tongue in snoring. The tongue is in a relaxed state when the individual is asleep on his back and is a factor in snoring. There is frequently a great deal of mental anguish connected with this sociologic problem and I believe if we could effectually control it, it would be a boon to mankind. Dr. Strauss should be congratulated on his sober interest in the matter. I have noted that snoring and disturbed sleep occasionally accompany an elongated uvula, but I have also observed patients with the uvula partly resected and yet the snoring factor had not been eliminated.

Dr. Walter Theobald: I have a patient, now 46 years of age, whose tonsils were removed at the age of 4 or 5 in the days when the uvula frequently got mixed up with the tonsil snare. The uvula was entirely absent; she had a fibrous and high archway of scar tissue.

I asked her if she snored and she said she did not know but had never been told she did. I think Dr. Salinger's suggestion might be used to find out whether the removal of the tonsils and uvula affects snoring.

DR. JEROME STRAUSS (closing): During the nine months since I have been carrying on this study in the laboratory and the office, I have looked at every palate and pharynx carefully. I am not sure that Dr. Ballenger is not correct, although I would be inclined to think the depth of the pharynx a more important factor.

CHICAGO LARYNGOLOGICAL AND OTOLOGICAL SOCIETY

Meeting of Monday, November 2, 1942

THE PRESIDENT, DR. G. HENRY MUNDT, IN THE CHAIR

Specific In Vitro Action of Sulfonamide Compounds on Pathogenic Organisms

MILAN NOVAK, M.D. (by invitation)

CHICAGO

(This paper appears in full on page 161 of this issue)

Pharmacological Development of the Sulfonamides and Their Action

FRANK T. MAHER, PH.D. (by invitation)

CHICAGO

(This paper appears in full on page 165 of this issue)

Clinical Experiences with Sulfonamides in Otolaryngology

GEORGE S. LIVINGSTON, M.D.

CHICAGO

(This paper appears in full on page 171 of this issue)

DISCUSSION

DR. THOMAS C. GALLOWAY: The question of the effect of sulfonamides on anaerobes is very interesting. Fox has shown that anaerobes do not respond to sulfonamides under lowered oxygen potentials. Meleney has shown, however, that in the presence of zinc peroxide one may get a good effect on anaerobes.

Manufacturers have been telling us lately that neoprontosil may be more effective than sulfanilamide. Is this so?

As much late damage was found after the use of dinitrophenol, I wonder if Dr. Maher could assure us that there is no danger of our waking up five or ten or fifteen years from now to find there have been some very serious and irreparable changes from the use of the sulfonamides.

It seems to me we are in an upward phase of complications with these drugs; I think we are finding more mastoid infections than in 1938-1940. At the Evanston Hospital we had 37 operated mastoids with 5 deaths in 1937; in 1938, after wide use of these drugs, we had 5 mastoid operations and no deaths. Now we are getting 10 to 12 mastoid infections a year but with very few fatalities. I have seen four cases recently in which physicians had unjustified confidence in the drug, gave it only three or four days, and after preliminary recession a more stubborn infection developed which required operation.

I have never been afraid of the masking effect. I know of no patient who died because sulfanilamide masked the symptoms. However, in one very striking case of sinus thrombosis which was masked the patient did not die but had a long illness which might have been avoided by earlier operation. I think we must learn more acuity in diagnosis, so we can allow for drug fever, simulated sepsis, etc., and when in doubt stop the drug and watch the effect.

Only lately I have learned that sulfathiazole can cause persistent and troublesome hemorrhage when the microcrystals are blown between the flaps after a submucous resection.

DR. SAMUEL SALINGER: My comments have to do with a very limited aspect of this subject, namely, the use of the sulfonamides as prophylactic agents against infection. In doing a number of rhinoplastic procedures over a period of years, I was always confronted with a certain number of postoperative infections which, though a small percentage of the total, are nevertheless always very distressing. The danger of infection is always present because the field, while presumably clean, is potentially infected. About a year ago I started using sulfathiazole, giving the usual average doses immediately after operation and continuing for four days. I have checked some 215 cases and was surprised to find that, despite this therapy, 17 cases had shown marked reaction, 7 of which developed pus and 10 a serosanguinous fluid. I have not had time to check a similar series in which the drug was not used, but my recollection

is that the incidence of reaction and suppuration would be about the same. Also, I noted a rather high percentage of toxic reaction; approximately 20 per cent of the series suffered from nausea and vomiting, occasionally so marked that the drug had to be withdrawn. I do not attribute the reaction entirely to sulfathiazole, as all patients received morphine and scopalamine preoperatively and this may have been a contributory factor.

I must confess some degree of disappointment, although I have the feeling that in the cases where a serosanguinous fluid was present, sulfathiazole may have prevented actual suppuration. Possibly the method of administration was faulty. At any rate, I expect to continue its use, with a closer analysis of the individual cases, and thereby obtain further information.

DR. ALFRED LEWY: The use of the sulfonamides in actinomycosis has not been referred to. A cure has been attributed to their use in a number of cases. It apparently has not been successful when the disease affected the bone, but if limited to soft tissue, the sulfonamides have been reported effective after the failure of iodides.

I was much interested in Dr. Livingston's discussion of the pros and cons of the use of these drugs in otitis media. He did not mention, however, that their use has given many otologists the courage to withhold surgery for a time and allow the mastoid to get well without it.

DR. JOHN R. LINDSAY: The work we reported at the recent meeting of the American Academy of Ophthalmology and Otolaryngology was confined primarily to the local use of tyrothricin and gramicidin in the upper respiratory tract, but since we had carried out clinical investigations with sulfathiazole, sodium sulfathiazole and sulfadiazine locally in this area, these were also reported. The work was done by several members of our staff as well as myself. Our experiences differed from those of Dr. Livingston. In the case of chronic suppuration of the sinuses including the maxillary, the frontal and the ethmoid sinuses, we were unable to satisfy ourselves that sulfathiazole used locally following irrigation was of any definite benefit. At that time we did not have the microcrystals but we did have suspensions of finely ground sulfathiazole, up to a concentration of 30 per cent, which could be introduced through a cannula. A small amount of hydrogen peroxide was added in some cases.

In treatment of acute sinus infection it may be well to remember that we are seldom dealing with a suppuration limited to one

sinus; there is usually more or less general upper respiratory infection with several sinuses involved. Therefore, the treatment of, for example, a maxillary sinus alone cannot be expected to relieve the accompanying inflammatory process in the anterior ethmoid and the frontal sinuses, or in the upper respiratory tract in general. That appears the one important reason why we did not find that the introduction of the sulfonamides into the sinuses following irrigation in the acute stages produced any appreciable shortening of the course of the disease. When this work was started some of our staff were much enthused with first impressions, but after a thorough trial we were unable to satisfy ourselves that the use of the sulfonamides in the sinus had any material effect in reducing the length or severity of the infection.

We began using a 2.5 per cent sulfadiazine spray (with triethanolamine) as described by Dr. Crowe at the annual Triological Society meeting. We have not used this as thoroughly as sulfathiazole, but, in our experience to the present, we have not been able to shorten the course of infections or demonstrate any appreciable effect as indicated on repeated cultures. This material was used in a few cases by the displacement method and produced fairly marked discomfort lasting nearly 24 hours. The pH is around 8.5 in this solution and attempts to lower the percentage of triethanolamine so as to reduce the pH caused precipitation.

The local use of sulfonamides does have a place, however, in postoperative treatment of sinuses which have been radically operated upon with removal of diseased mucosa. The effects here are similar to those in surgical wounds elsewhere and the effect in keeping down infection is unmistakable. Whether or not there is slight irritation probably is of secondary importance.

In the treatment of really severe acute sinusitis the method of choice in our opinion is the parenteral use of sulfonamides in adequate concentration. This is the most effective way to prevent the progress and spread of such infections. Local interference to effect removal of a collection of pus may still be necessary but will be rendered more safe.

DR. A. R. HOLLENDER: Radiation is not compatible with the administration of the sulfonamides. I have observed two patients with severe toxic reactions resulting from the use of x-radiation while the drug was being taken. Radiation implies any and all sources of radiation energy from x-rays to the sun's rays. From what I have seen, I deplore the prescribing of sulfonamide drugs for ambulatory

patients. There are other reasons for this; we frequently contribute to the incidence of toxic reactions by lack of knowledge of incompatibilities.

DR. GLENN GREENWOOD: I was interested in a comment I heard at the Academy to the effect that a Committee of the National Research Council found that applying sulfonamides to clean wounds caused delay in healing as compared with controls. I have had experiences in the use of sulfonamide solutions in the nose comparable to those of Dr. Lindsay. In some cases the discomfort has been so great that I have used a mild local anesthetic solution prior to the administration of these compounds. I believe solutions should be used that are compatible, or approximately so, with the pH of the nasal secretions. The effect of these agents in the nose to date has been, in my experience, more detrimental than advantageous.

DR. NOAH D. FABRICANT: Several weeks ago I saw a report of several papers given at the meeting of the American Chemical Society. One of the papers advanced an interesting thesis. While the discussion did not include the local application of sulfonamides, in general it was claimed that the therapeutic efficacy of all sulfonamides was definitely related to the pH. If sulfonamides are alkaline they are not desirable; if too acid they are also not desirable; but if properly acid they are most satisfactory. I wrote and asked if this thesis had been correctly reported and the authors replied they would send me their findings in detail.

DR. WALTER H. THEOBALD: I should like to bear out Dr. Galloway's experience with hemorrhage. This was the interest we had in determining whether or not the sulfonamides would have an influence on healing in the tonsillar fossae following tonsillectomy. The drug was used in one fossa and not in the other, as a control. However, our observations seemed to indicate that it stimulated or promoted bleeding in the side which was treated by sulfonamides as compared to the nontreated side.

DR. MILAN NOVAK (closing): In connection with the effectiveness of sulfonamide therapy in actinomycosis, I might state the results of some laboratory observations we have made. The pathogenic Actinomyces in general are difficult to maintain in culture for more than a month so that fresh strains must be frequently isolated from human or bovine sources (lumpy jaw in cattle). Experiments on two human strains of Actinomyces bovis and several strains isolated from infected jawbones of cattle showed that every small quantities of the drugs completely inhibit growth in the test tube. Concentra-

tions as low as .5 mgm. per 100 cc. of sulfanilamide or sulfathiazole are effective.

Several reports in the literature indicate that varied results are obtained in actual treatment of human infections. The probable explanation is in the presence of a greater amount of purulent material in one case as compared to another. The effect of sulfonamides is definitely decreased in the presence of necrotic material and much higher concentrations, 100 mgm. per 100 cc. or more, are required to demonstrate an inhibitory effect on the organism. The logical treatment of actinomycosis would therefore resolve itself into a combined surgical treatment by thorough curettement followed by local application of sulfonamides to obtain a high local concentration.

DR. FRANK T. MAHER (closing): The effect of peroxidases and oxidases goes back to 1939, when Shaffer indicated that one action of the sulfonamide drugs was to inhibit certain peroxidase enzymes which break down bacteria. A series of papers in 1939-1941 showed the inhibition of these types of enzymes. A year or so ago I found about 15 different theories of the mechanism of action, among them that sulfonamides are effective because they inhibit catalase. That theory has fallen in disrepute at the present time. They were not able to demonstrate the significance of catalase inhibition to the mechanism of sulfonamide chemotherapy. A number of organisms which do not come into the picture are sensitive to the action of the sulfonamides, but are not peroxide producers; also, a number which are, are not particularly susceptible to sulfonamides. At the present time the theory is that of enzyme inhibition, which began about 1938 with Lockwood's studies on the effect of peptone, extended by current studies with p-amino benzoic acid. The defense mechanisms of the host play an important role, according to our studies.

Neoprontosil probably represents the last development of sulfonamide of the azo type; the original group were azo derivatives and for a long time they were the only type in practice. The French had difficulty in getting the compounds out of Germany, and developed their own compounds, diazo compounds, which are comparable to neoprontosil. There is an international variation. So far as American therapeutics are concerned, neoprontosil action is the same as sulfanilamide. It is less toxic; there is a lower incidence of nausea and vomiting; it can be used sometimes when sulfanilamide is not well received; it is a more soluble compound; it offers a more concentrated solution for subcutaneous or intramuscular administration. The belief exists in certain quarters that results are obtained with

diazo compounds which cannot be obtained with simple compounds of the sulfonamide type. We are not able to confirm that.

Botanists say that any time a chemical drug is synthesized, sooner or later there will be some undesirable effect. That was particularly true of dinitrophenol. It might be the effect of stepping up metabolism. We have had the sulfonamides in action for ten years, actively for five or six years, and so far as I know there are no examples of hidden toxicity. That does not mean one may not come up.

As to the question of pH: if you look at the chemical formula for sulfanilamide it has the basic amino grouping balanced by the acidic amido grouping. One German writer has postulated that this chemical balance is important. Studies in urinary infections have shown that sulfonamides are clinically effective over a range in pH from the acid to the alkaline side.

Dr. George S. Livingston (closing): The danger of masking is that someone not trained in observation may be handling a certain case, but I think this should not deter us from the use of the sulfonamides. I do not feel that although there was improvement and cessation of discharge in chronic sinusitis, I really cured it. I think it is usually complicated by some constitutional condition, especially by allergy. If one achieves favorable results, the next head cold may start suppuration again because the membrane never had returned to normal.

As to the discomfort, I have had no patients complain when I used microcrystals; I have not used a 2.5 per cent solution of sodium sulfathiazole.

There have been many articles recently for and against delayed healing when sulfonamides are used locally. It may be related to a foreign body reaction in the tissues. In a recent article by Taylor in the Journal of the American Medical Association it is reported that a large amount of reaction occurred around the site of implantation of sulfanilamide crystals; others have reported no reaction. Chambers reported no evidence of the drug ten days after implantation. I found no difficulty with healing in the mastoid; perhaps in abdominal wounds the problem is different.

As to the pH, the only citation I had was Silcox and Schenck, who stated that the microcrystals have a pH which is physiologically compatible with the respiratory tract mucosa. A recent article from the Mayo Clinic reported the use of various compounds, and stated

that sulfanilamide, sulfathiazole and sulfaguanidine were none of them hemostatic; sulfapyridine used locally was found to be hemostatic. At Children's Memorial Hospital I used it routinely in the nasopharynx after adenoid operation on about 100 cases; there was no appreciable difference in the number of postoperative hemorrhages.

I would like to emphasize sensitivity. If this proves to be a true hypersensitization, and if the increasingly widespread use of sulfonamides continues, we can probably look forward to a much greater number of toxic reactions as time goes on. The literature I reviewed states that many toxic reactions are likely to occur, increasingly so after the initial course; something like 2.5 per cent have been reported on initial administration; 36 per cent on the second course; and 80 per cent on the third. With continued repeated administration of small doses there seems to be a tendency for the reaction to be less severe.

Abstracts of Current Articles

NOSE

The Nasal Entrance.

McKenzie, W. Raymond, South. M. J. 35:433-441 (May) 1942.

The number of deformities and obstructions occurring at the nasal entrance is truly amazing, as the author has observed them in 50 to 75 per cent of the men being inducted into the services. Information concerning this subject is found in textbooks on rhinoplastic surgery and in recent journals but not in rhinologic textbooks. However he feels that as these deformities are so frequently associated with septal deflections and nasal obstruction, it is entirely a rhinologic problem, and should be corrected by a rhinologist. It is important to examine the nose without a speculum first, as many deformities will be overlooked or so distorted by displacement with the speculum that they will not be recognized. He illustrates and briefly describes methods of correcting the following deformities: curling or deflection of the anterior edge of the septal cartilage, curving or deflected anterior portion of the septal cartilage, thickened columella, elongated columella, deflected columella, eversion of the medial crura, collapse of the triangular and lateral crura of the alar cartilages, and prominent or bulbous tip. When required, submucous resection of the septum can usually be done through the same incision.

BRYAN.

Odors (Osmyls) as Allergenic Agents.

Urbach, Erich, J. Allergy 13:387-396 (May) 1942.

That odors (osmyls) are due to particles that emanate from odoriferous substances and strike upon the nasal membranes was proved by the French scientist Devaux.

The author cites much evidence to show that these particles may cause rhinorrhea or asthma in the absence of pollen granules.

Pollen allergy can be excluded in the instances of grafted flowers which have no stamens, flowers whose stamens are situated so

that pollen cannot be carried by the wind, or when the insufflation of pollen into the nose causes no symptoms.

In two patients with a strictly monovalent hypersensitiveness to sage tea the author was able to prove, by the use of chemical fractionation, that the odors contained in the sage plant represent the allergen.

Numerous examples of patients being sensitive to animal odors are given.

The author observed instances of specific sensitiveness to inorganic synthetic perfumes, to the sulfuric emanation of a sulfur spa, and other authors are quoted who have studied urticaria due to the oxidation of fats and sensitivity to varieties of smoke.

The therapeutic results achieved by the oral administration of minute doses of odoriferous substances and volatile oils support the evidence that the allergen is represented by the osmyl.

DEAN, JR.

Vitamins for the Prevention of Colds.

Cowan, Donald W., Diehl, Harold S., and Baker, A. B., J. A. M. A. 120:1268-1271 (Dec. 19) 1942.

This work represents further studies on the prevention of colds in students of the University of Minnesota who volunteered because they were particularly susceptible to colds.

During the winter of 1939-1940, 427 students volunteered. Some were given synthetic ascorbic acid, 200 mg. daily; others were given 200 mg. daily for two weeks followed by 100 mg. daily, but in the event of a cold were to take 500 mg. for two days. A third group were given placebo tablets. Those taking vitamin C showed a 65.5 per cent reduction in colds, while those taking placebo tablets showed a 62.7 per cent reduction.

During the winter of 1940-1941, 264 students were studied. Those who took multiple vitamin capsules and those who were given placebo capsules experienced colds equal in number, severity and duration.

DEAN, JR.

ESOPHAGUS

Multiple Polyps of the Esophagus. Report of a Case with Complicating Recurrent Gastrointestinal Hemorrhages.

Dickes, R., Knudsen, A. F., and Franco, S. C., Arch. Int. Med., 70:121, 1942.

In this remarkable case the clinical findings were very suggestive of Banti's syndrome so that one would expect that esophageal varices probably were the cause of hemorrhage. However, numerous esophagoscopic examinations demonstrated the rare condition of multiple polyposis. The polyps were very vascular, so that about one and a half liters of blood were lost after biopsy. Cure was brought about by fulguration.

HARFORD.

EAR

A Device for Detecting Simulated Unilateral Deafness.

Pitman, Major Louis K., J. A. M. A. 121:752-753 (Mar. 6) 1943.

The device used is a two-in-one petcock set in the fork of a stethoscope. With the stethoscope adjusted to the suspect's ears with the bell behind his back, the noise of a Bárány noise apparatus may be directed to one ear while the examiner's voice is directed to the other. The petcock handle is moved so as to quickly interchange the voice and Bárány apparatus from ear to ear, the resulting effect confusing a malingerer helplessly.

DEAN, JR.

Vertigo Due to Obstruction of the Eustachian Tubes.

Merica, F. W., J. A. M. A. 118:1282 (Apr. 11) 1942.

The author discusses the findings in 135 cases of vertigo due to tubal obstruction. Many of the patients had associated acute or chronic disease of the sinuses or ears. In 15 instances the condition was associated with colds.

Some patients obtained immediate dramatic relief from severe vertigo after inflation of the eustachian tubes. Some patients derived permanent relief from one inflation; others had recurrence of symptoms and required repeated treatments.

The author's method of treatment consists of catheterization, bouginage and bulb inflation.

Some patients with eustachian tube obstruction proved to be allergic and improved when the offending allergen was recognized and eliminated. Patients with a low metabolic rate had improved tubal patency after the administration of thyroid.

DEAN, JR.

The Effects on Hearing of Acoustic Trauma in Industry and War.

Fox, Samuel L., South. M. J. 36:97-100 (Feb.) 1943.

Occupational deafness is divided into three types: (1) explosion deafness in which there is sudden and almost always permanent partial loss of all tones or occasionally the high tones, (2) chronic noise deafness resulting from continued exposure to loud noises and showing a progressive deafness which is reversible only if recognized and guarded against early, and (3) air pressure (caisson) deafness following sudden changes in pressure accompanied by acute deafness, vertigo, faintness, vomiting, tinnitus and occasionally hemorrhage from the ear.

The author recognizes the importance of protecting the employee by mechanical insulation and protecting the employer by the use of audiograms for prospective workers as well as re-examination once a year.

DEAN, JR.

MISCELLANEOUS

Infectious Neuronitis. Review of Literature and Presentation of Four Cases.

Fox, M. J., and O'Connor, R. D., Arch. Int. Med., 69:58, 1942.

This syndrome is called infectious because prodromal symptoms usually suggest an infection and not because an etiological agent has been established. There is an ascending paralysis but the prognosis is usually good in that function of muscles returns. Sensory abnormalities are sometimes present. Probably the most characteristic feature of the syndrome is the albuminocytologic dissociation; that is, the spinal fluid contains increased protein (usually over 300 mg.

per 100 cc.) in the presence of a normal cell count. The condition is also known as the Guillain-Barré syndrome.

HARFORD.

Chemotherapy and Chemoserotherapy of Staphylococcic Infections.

Kolmer, J. A., and Brown, H., Arch. Int. Med., 69:636, 1942.

This is a report of experiments designed to demonstrate the effect of certain chemicals and antiserum on experimental staphylococcal infections in mice and rabbits. The protocols demonstrate again that such experiments are much less decisive than similar experiments using streptococci or pneumococci. It is difficult to infect animals with staphylococci and the effect of chemicals or antisera is much less striking, since complete recovery from abscesses is frequently not obtained. Some investigators even deny the validity of such experiments. The authors concluded that chemotherapy in the form of sulfathiazole or sulfapyridine used in combination with staphylococcus antitoxin is of more value than either chemotherapy or serotherapy alone but that specific treatment of these infections is far from satisfactory.

HARFORD.

Induced Thiamine (Vitamin B_1) Deficiency and the Thiamine Requirement of Man: Further Observations.

Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M., Arch. Int. Med. 69:721, 1942.

In a previous communication, these workers reported the effects of severe thiamine deficiency on human beings. Now they report the results obtained when 11 women were placed on a diet slightly deficient in thiamine and approximately the same as that taken by some American families. The subjects developed a number of readily observed psychiatric and metabolic abnormalities. These changes were reversed to normal in half the patients by administration of thiamine without their knowing it. This work has not only given valuable information on the clinical findings in a borderline state of thiamine deficiency but has indicated that the requirement, as judged by the amount necessary to prevent clinical manifestations, is not less than 0.5 mg. nor more than 1.0 mg. for each 1000 calories in the diet.

HARFORD.

Clinical Studies of Drug Addiction, Physical Dependence, Withdrawal and Recovery.

Himmelsbach, C. K., Arch Int. Med., 69:766, 1942.

In 21 morphine addicts, objective observations were made before, during, and at intervals after, withdrawal of the drug. It was found that physical adjustment to morphine is incomplete although the patient appears normal. After withdrawal of the drug, recovery requires about six months. A simple measure of recovery is failure to gain further weight.

HARFORD.

Distribution of Specific Types of Hemolytic Streptococci in Eight Hundred and Nineteen Cases of Infection.

Keefer, C. S., Rantz, L. A., Shuman, H. H., and Rammelkamp, C. H., Arch. Int. Med. 69:952, 1942.

This paper is a report of the clinical application of immunological methods for the classification of hemolytic streptococci. Strains were obtained from many different kinds of human disease caused by these organisms and so this study concerned itself only with strains in Group A as designated by Lancefield. These were subdivided into 29 types by a slide agglutination method described by Griffith.

The results of this work, combined with previous reports in the literature, indicated that the evidence does not permit the conclusion that certain specific types are more likely to cause human disease than others. It has also shown that organisms of one type may be the cause of any of the clinical varieties of infection, such as scarlet fever, puerperal fever, tonsillitis, or erysipelas. Multiple infections occurring in families or institutions are usually due to the same type regardless of the clinical form of the disease. Epidemics have been traced to a single infected individual. In the complications of scarlet fever, those occurring during the first two weeks are usually caused by the same type as that causing the original disease, those coming later are frequently due to another type.

Although sulfonamide therapy has reduced the morbidity and mortality of hemolytic streptococcal infections very greatly, the desirability of further preventing their occurrence must be obvious. The chief value of typing of strains of these organisms lies in a study

of their modes of transmission and in that way contributes to their ultimate prevention.

HARFORD.

Hyperactive Vasodepressor Carotid Sinus Reflex.

Sigler, L. H., Arch. Int. Med., 70:983, 1942.

It is well known that sensory receptor end-organs are present in the carotid sinus, the stimulation of which results in the slowing of the rate of the heart or the lowering of blood pressure or both. This reflex is initiated under physiological conditions by the elevation of blood pressure and constitutes a mechanism whereby blood pressure is automatically regulated. The reflex may also be brought about by manual compression of the sinus. The automatic regulation of blood pressure by this mechanism goes on constantly so that the theory has arisen that essential hypertension in man is due to a defect in the reflex. If this were so, the vasodepressor reflex should not be obtainable in patients with hypertension. The author has obtained further evidence that this theory is not valid by a study of the blood pressure in 700 patients after manual pressure on the carotid sinus. In agreement with others, he finds that blood pressure is more apt to fall in patients with hypertension and the fall is usually greater. He also finds that activity of the reflex increases with age and is found more frequently in males than females.

HARFORD.

Neck Pain: The Laminagraph as an Aid to the Diagnosis of Atlanto-Occipital Injuries.

Jostes, Frederick A., J. A. M. A. 118:353 (Jan. 31) 1942.

Prior to the development of body section roentgenography the diseases of the upper cervical spine causing pain in the neck and shoulders were poorly understood. It is now possible to demonstrate this area in a satisfactory manner which the former conventional spine films failed to achieve.

Asymmetry of the occipital condyles, subluxation of the atlanto-occipital joints, irregularities or fractures of the atlas or odontoid process and arthritis of the upper cervical spine are some of the pathological processes most commonly encountered.

Case histories and x-rays are included to illustrate these lesions.

DEAN, JR.

Fatalities and Constitutional Reactions Following the Use of Pontocaine.

Thomas, J. Warrick, and Fenton, Meryl M., J. Allergy 14:145-159 (Jan.) 1943.

The fatalities and reactions previously described in the literature are reviewed and nine new cases with three deaths are presented. The nine new cases occurred during preparation for bronchoscopy, gastroscopy or bronchography.

Patients with allergy, emaciation, cardiac or thyroid disease, endocrine disorders and those with open wounds or traumatized areas which would permit easy entrance of the local anesthetic into the blood stream should be given pontocaine with caution, as patients in this group are most likely to have unfavorable reactions. Patients should be questioned concerning previous reactions and, if there is doubt, a patch test may prove helpful.

Since both pontocaine and procaine contain a para-amino benzoyl group, it is suggested that a patient sensitive to one is likely to be sensitive to the other. One case report bears this out. Cocaine contains a benzoyl group and should be a safe anesthetic for a patient sensitive to pontocaine.

Drugs to be used as emergency measures when reactions occur include epinephrin, caffeine sodio-benzoate, and caffeine as stimulants; sodium phenobarbital intravenously controls muscular twitching and convulsions; carbon dioxide and oxygen mixtures stimulate respiration.

DEAN, JR.

Books Received

Surgery of the Nose and Throat.

By John Devereux Kernan, M.D., Editor, Professor of Otolaryngology, College of Physicians and Surgeons, Columbia University; Attending Otolaryngologist and Bronchoscopist, Lenox Hill Hospital. Contributors: George Renfrew Brighton, New York; Assistant Clinical Professor of Otolaryngology, College of Physicians and Surgeons, Columbia University; Attending Otolaryngologist, Presbyterian Hospital, Babies Hospital, and Vanderbilt Clinic. James Barret Brown, St. Louis; Lieutenant-Colonel, Medical Corps, United States Army; Associate Professor of Clinical Surgery, Washington University School of Medicine. Arthur J. Cracovaner, New York; Instructor of Otolaryngology, College of Physicians and Surgeons, Columbia University; Associate Otolaryngologist, Lenox Hill Hospital; Assistant Otolaryngologist, Presbyterian Hospital, Vanderbilt Clinic, and Babies Hospital. Andrew A. Eggston, New York; Director of the Laboratory and Consulting Physician, Manhattan Eye and Ear Hospital; Pathologist and Bacteriologist for the City of Mount Vernon; Consulting Physician, Mount Vernon Hospital. Chevalier L. Jackson, Philadelphia; Professor of Broncho-Esophagology, Temple University School of Medicine and Hospital; Bronchoscopist to the Lankenau Hospital and Mary J. Drexel Home, Chestnut Hill Hospital, Eagleville Sanatorium and Hospital. John Devereux Kernan, New York. Hayes Martin, New York; Assistant Professor of Clinical Surgery, Cornell University Medical College; Attending Surgeon, Memorial Hospital. Harry Neivert, New York; Assistant Clinical Professor of Otolaryngology, College of Physicians and Surgeons, Columbia University; Attending Otolaryngologist, Presbyterian Hospital, Vanderbilt Clinic, and Babies Hospital; Junior Surgeon, Manhattan Eye and Ear Hospital. Henry Boylan Orton, Newark; Professor of Laryngeal Surgery, New York Polyclinic Medical School; Attending Surgeon, Department of Laryngology, Rhinology and Bronchology, Presbyterian Hospital; Attending Laryngeal Surgeon and Broncho-Esophagologist, St. Michael's Hospital. Pp. vii + 701, with 616 illustrations, 3 colored plates, and 10 tables. New York, Thomas Nelson and Sons, 1942.

A very excellent text.

Two qualities appear to characterize this book as one first pages through it: clarity and completeness. The material is laid down in an orderly manner, controversial methods are largely omitted and there is nowhere the tendency to superficiality which pervades some others of the contemporary texts. These authors have dealt dispassionately with their subjects and have largely avoided overemphasis of their personal leanings.

On closer reading one encounters a balance of judgment and an authenticity which renders this a valuable handbook for graduate students, house-officers and younger laryngologists. The chapter on Histopathology is especially recommended.

One takes occasion here to do homage to J. Parsons Schaeffer. After twenty-three years the best authors still agree that the finest anatomical fare which can be served up to their readers comes bodily from Schaeffer's text. Neivert wisely quotes him in extenso and reproduces 22 of his classical illustrations. He writes in his Introduction "At that time (1923) I suggested to Dr. Schaeffer that he get someone to write a supplementary volume to his monumental work *The Nose, Paranasal Sinuses, Nasolacrimal Passageways, and Olfactory Organ*, dealing with the diseases of the nose and their treatment. He felt that because embryology and anatomy are so static, and because treatment of diseases is so changeable, it would scarcely be feasible." Rhinologists know now that that static quality is attributable largely to the untiring application to detail and the scrupulous honesty of Schaeffer himself.

War Medicine.

Edited by Winfield Scott Pugh, Commander (M.C.) U.S.N., Retired, Formerly Surgeon City Hospital, New York; Edward Podolsky, M.D.; and Dagobert D. Runes, Ph.D. Pp. 565, illustrated. New York, Philosophical Library, 1942. (Price $7.50.)

This is a collection of more than fifty essays upon conditions, diseases and injuries of modern warfare, in civilians and combatants on land, on and under water, and in the air. They are by as many authors, and are gleaned and reprinted from many journals.

Descriptions of these conditions—they range from gunshot wounds of the brain to chigger-bites—are characterized by directness, brevity and above all, practicality. Many of the authors are on active service with the British and the American armed forces.

Despite the title, one half the book is devoted to surgical subjects, and some hundred pages deal with aviation problems. Beside chapters bearing upon the more usual phases of infection, wound healing, typical injuries and diseases are such subjects as The Treatment of Burns, The Danger to the Hearing Apparatus, Lung Injuries Due to the Detonation of High Explosives, Blood Substitutes, "March Fractures", High Altitude Flying and Deep Sea Diving, Liquefaction of Solid Foodstuffs for Diets, and Malingering.

Diseases and Injuries of the Larynx.

Chevalier Jackson, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-Esophagology, Temple University, Philadelphia; and Chevalier L. Jackson, A.B., M.D., M.Sc., (Med.), F.A.C.S., Temple University, Philadelphia. (2d Edition.) Pp. 1-633, with 200 illustrations, 11 in color. New York, The Macmillan Co., 1942. (Price $8.00.)

With their usual conciseness and passion for detail the Jacksons, father and son, have augmented to a six-hundred-page volume their "Larynx and its Diseases," first published in 1937. The material is again presented in textbook style, suited at once to intensive study and to the quick reference which derangements of the airway are apt to call for.

Each condition is minutely described in a vivid and direct manner. Paper, print and illustrations are of the first order.

The extent to which these authors have contributed to the subject in past years through their labors may be measured by the fact that almost two-thirds of the items listed in the Table of References refer to their own previous publications.

Manual of Oxygen Therapy Techniques (including Carbon Dioxide, Helium and Water Vapor).

By Albert H. Andrews, Jr., M.D., Director, Oxygen Therapy Department and Assistant Attending Otolaryngologist, St. Luke's Hospital, Chicago; Instructor in Laryngology, Rhinology and Otology (Broncho-esophagology), University of Illinois College of Medicine; Associate Attending Broncho-esophagologist, Children's Memorial Hospital, Chicago; Former Research Instructor, Department of Physiology and Pharmacology, Northwestern University Medical School. Pp. 191, with 33 illustrations and 16 tables. Chicago, The Year Book Publishers, Inc., 1943 (Price $1.75).

On the borderlines of therapy are numerous procedures which if first encountered after the age of interneship are taken more or less for granted until the occasion arises when one is confronted with the necessity of applying them. Then all at once it appears that there are a right way and forty wrong ways of proceeding. One of these, to many of us, is oxygen therapy.

Andrews covers the handling of oxygen from factory to lung in a practical and detailed manner, including such information as piping systems, safety precautions, masks, tents and cannulae.

The contents of the chapter on the "Open Top Oxygen Tent," chosen at random from the twenty-seven, typifies the scope of the book: Orders, Equipment, Directions for Starting, Criteria of Effective Technique, Directions for Routine Care, Open Top Tent with Cover, Open Top Tent for Children.

"A technical handbook rather than . . . a medical textbook."

Nasal Medication, A Practical Guide.

By Noah D. Fabricant, M.D., M.S., Associate in Laryngology, Rhinology and Otology, University of Illinois, College of Medicine. Pp. ix, 1-122, with 20 ills. Baltimore, Williams and Wilkins Co., 1942 (Price $2.50).

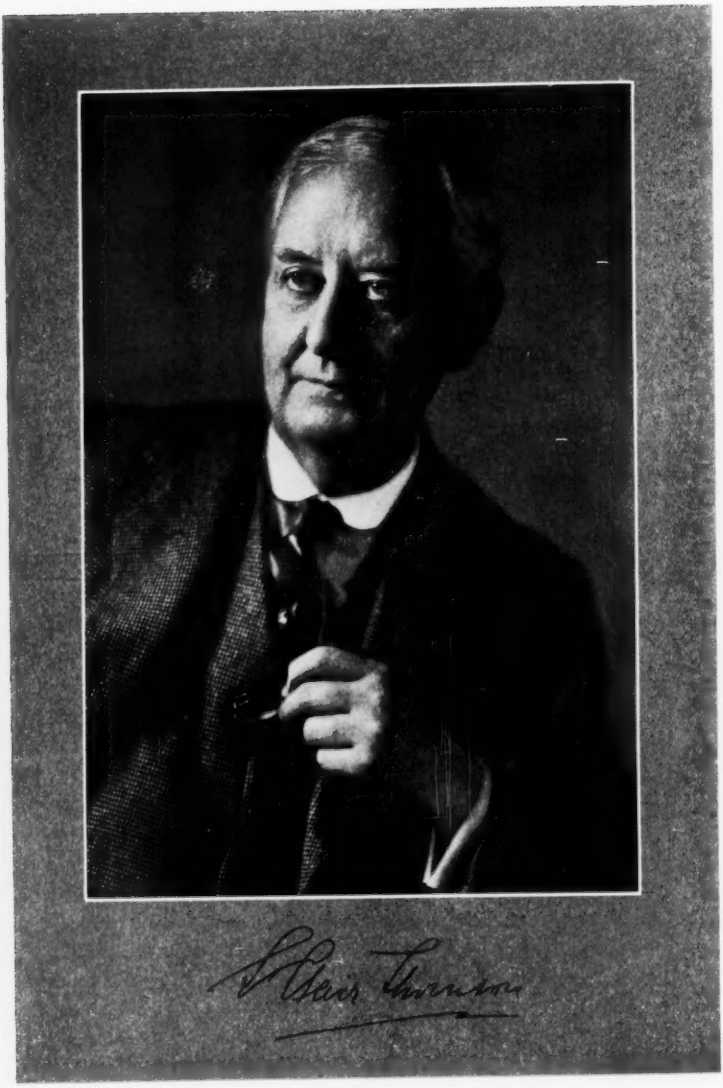
The first forty pages of this book deal with nasal anatomy, histology and physiology; the second forty with the effects of drugs and their application; the third with medication under the headings: The Common Cold, Sinusitis, Nasal Allergy, Hypertrophic Rhinitis, Atrophic Rhinitis, Sphenopalatine Ganglion Neuralgia, Vestibulitis, Nasal Immunization.

The specialist reasonably familiar with the literature will not find much here which is new to him, but it should serve, to quote the author, "as a practical guide for physicians . . . and for those who employ nasal medication."

Ear, Nose and Throat Nursing.

By James Hardie Neil, D.S.O., C. de G., F.R.A.C.S., F.A.C.S., Ear, Nose and Throat Surgeon, Auckland Hospital, and Mater Misericordiae Hospital, Auckland; Past President Pan-Pacific Surgical Congress. Ed. 3, pp. 126, illustrated. Auckland, Clark & Matheson, Ltd., Auckland, 1942.

A small, informative booklet by a leading laryngologist which will receive the interested attention of our nurses now in the South Pacific.



SIR ST. CLAIR THOMSON, M.D., F.R.C.P., F.R.C.S.

1859-1943

Sir St. Clair Thomson, dean of British laryngologists, died at Edinburgh on January 29, at the age of 83. Probably no other laryngologist, of this century at least, has enjoyed the wide acquaintanceship and the general acclaim that were his. This was due partly to the untiring zeal and lifelong passion for clinical observation which are manifest in his writings and partly to his facility as a linguist, which made him a prominent figure at the numerous international congresses.

To the British Medical Journal we are indebted for the following sketch of his life. It recounts that . . .

"Although St. Clair Thomson was born at Londonderry in 1859, his father was an Argyllshire man from the village of Ardrishaig on Loch Glip. The 'St. Clair' in his son's name was from his maternal grandfather, John Sinclair of the Sound of Mull. When he was 19 St. Clair Thomson entered as a junior scholar in the medical division of King's College, London. He took the M.R.C.S. and L.S.A. in 1881, and at the M.B. London examination in 1883 he obtained honours in medicine. He then became house-surgeon at King's College Hospital, where his chief was Joseph Lister, who had entered it as a student. St. Clair Thomson was never tired of recalling his great master. . . .

"St. Clair Thomson completed his training in Vienna, Paris, and Lausanne, making acquaintance with foreign surgeons and their methods and establishing his knowledge of laryngology. At King's College Hospital at the time he was a student the teaching in this subject was wholly inadequate. He once said that when he gained his degree in medicine he had never seen the vocal cords—or the drum of the ear—in the living person. . . .

"In Vienna one of his great teachers was Hajek, afterwards professor of laryngology and rhinology at the University there, but then a privat-docent. . . . It was Hajek who taught him the importance not only of looking at specimens but of handling them and making his own sections. Thomson also worked in Vienna with von Schrotter, Stoerk, and Politzer. . . .

"In 1893 he returned to London and took the F.R.C.S. He had already taken the London M.D. in 1888, and also the M.D. of Lausanne in 1891. He became physician to the Throat Hospital, Golden Square, and surgeon to the Royal Ear Hospital. In 1901 he was appointed assistant physician for diseases of the throat and nose at his old hospital, King's College, where his department had two beds in the male and two in the female surgical wards, but no special theatre, a room being fitted up for operations. In 1903 he was elected F.R.C.P. In 1905 he became physician in charge of the department, and in 1908 professor of laryngology at King's College. . . . He continued to hold the two appointments until his retirement in 1924 at the age of 65, when he was made consulting surgeon and emeritus professor. His connection with King's College, so long distinguished, was further marked by his election to the Fellowship of the College in 1927, and by the unani-

mous choice of him for the chair of the past and present students' centenary celebrations in 1930. . . .

"One subject to which he devoted himself in particular was intrinsic cancer of the larynx. . . . Laryngofissure, from being an operation with a high mortality, was made safe by improvements in early diagnosis and technique, and this advance was due in large measure to his work. . . . In 1930, with Mr. Lionel Colledge as co-author, he published a book on this subject.

"Tuberculosis of the larynx was also one of his great interests, and in a work from his pen in 1924 he described about 2,500 cases which he had seen during thirteen years. . . .

"His famous textbook, *Diseases of the Nose and Throat*, first appeared in 1911, a second edition in 1916, a third in 1926, and a fourth, in which he was assisted by Mr. V. E. Negus, in 1937. . . . His first publication was in 1895—a translation of Onodi's *Anatomy of the Nasal Cavity*. Among appointments other than those already mentioned which he held at various times were those of surgeon to the throat and ear department of the Dreadnought Hospital, Greenwich, professor of laryngology and otology at the Royal Army Medical College, consulting throat physician to the Actors' and Music Hall Artistes' Associations, and physician to the Royal Italian Opera.

"In 1913, when the International Medical Congress was held in London, Sir St. Clair Thomson—he had received his knighthood in the previous year—was president of the Section of Laryngology, and his command of languages enabled him to welcome each national group of delegates in its own. In 1918 he was president of the Medical Society of London and in 1924-6 president of the Royal Society of Medicine . . .

"St. Clair Thomson was a corresponding honorary member of most of the laryngological societies of Europe and of the American Laryngological Association. In 1936 the Académie de Médecine of Paris unanimously promoted him, already a Foreign Correspondent, to be a Foreign Associate. Among other noteworthy decorations which he was entitled to wear were the swords of a Commander of the Order of Leopold, the ribbon of an Officer of the Legion of Honour, and the medal of the Reconnaissance Française. On the occasion of the visit of the British Medical Association to Canada in 1930, when he was president of the Section of Laryngology, he received at the Convocation of the University of Manitoba the honorary degree of LL.D. He was president of the same Section at Belfast in 1909 and at the Centenary Meeting in London in 1932. A recognition which perhaps pleased him most of all was the gift from 175 of his fellow laryngologists of a loving cup, which was presented to him in 1926. . . .

"Sir St. Clair Thomson was a widower, his wife, whom he had married in 1900, having died in 1905."

The death of this great man has called forth many tributes and reminiscences from his colleagues and from patients and friends in all parts of the world. Not a few American laryngologists visiting London will recall with some warmth that even in his advanced years it was his pleasure to constitute himself guide and host, and to make it his personal concern to see that the visitor was kept informed of operations and other occurrences which might be of inter-

est to him. Cards kept appearing at one's hotel bearing memoranda of such happenings and signed in his familiar fine hand.

Luncheon at his home, No. 64 Wimpole Street, was an occasion. Surrounded by his friends and a fine collection of art treasures which he had enthusiastically assembled—he had a special penchant for miniatures—he was at his best. Always vivacious and alert he kept the conversation in a high key of good humor.

During one of the revisions of his textbook, neat piles of typed sheets would be heaped on chairs and tables and on every other available article of furniture. This book which came to be known as the "Laryngologist's Bible" was remarkable for its simplicity and completeness, but above all for its thorough documentation. Every observation was as authoritative as a wide and discriminating familiarity with the literature could make it. At the time of his tragic death the author was engaged in the preparation of a fifth edition.

In a letter dated June 7, 1942, he wrote from Edinburgh: "You have probably not heard that I have lost my house in London 'through enemy action,' and, as I am too old for war work and would only be in the way in London, I have retreated here 'for the duration'. I am well lodged and well fed and, in spite of years, keep very fair health.

"To employ my leisure it has fortunately happened that the publishers have written to say they want, even in war time, a new edition of my Text Book, as their last issue is nearly exhausted.

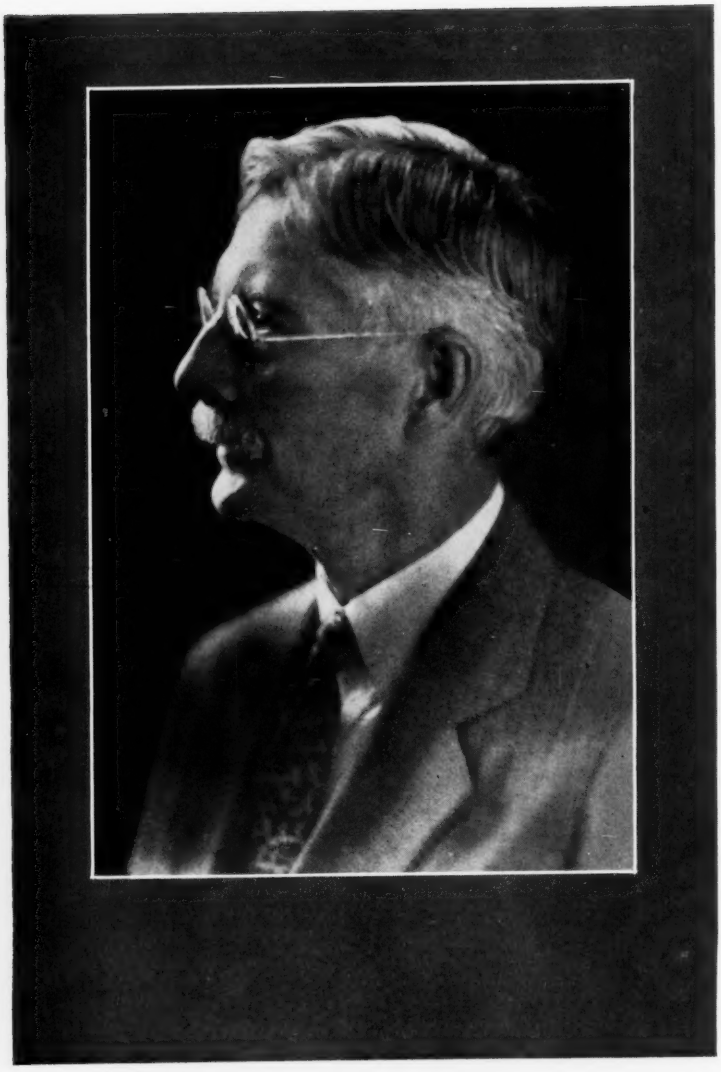
"Going through it I find so many changes and such progress in the last seven years that I see I have my job cut out!

"I am just at the early chapters on 'Treatment' and 'Medication' and see that I must jettison a lot of junk which was put in to please the public, then devoted to 'treatments' to the nose from a very imposing Spray Apparatus! I was never a believer in it from the early days when I devoted some attention to the 'defences of the upper air passages.' "

Then follows a discussion of these "defences" displaying an interest in, and a curiosity regarding, some current investigations which bespoke a mind undaunted and undamped by age.

His was the last among the great names associated with the early development and foundation of our specialty. The changing panorama of medical education in our day will not reveal many like them.

A. W. P.



JOHN F. BARNHILL, M.D., LL.D.

1865-1943

John F. Barnhill, who died on March 10, 1943, at Miami Beach, Florida, was born January 2, 1865, near Flora, Illinois. A few years later, his family moved first to Missouri and then to Indiana, where their young son entered the common schools. Dr. Barnhill attended Union High School at Westfield, Indiana, and graduated from Central Normal College at Danville, Indiana. He was graduated in medicine from the Central College of Physicians and Surgeons at Indianapolis, which later became affiliated with the Indiana University School of Medicine. Upon graduation he served his interneship (1888-89) at the City Dispensary in Indianapolis, becoming associated with Dr. Eastman at the Eastman Sanitarium, and later with Dr. Robert Long of Indianapolis.

During the first few years after his graduation from medical school (1889-95) he engaged in the practice of general medicine, subsequently limiting himself to otolaryngology and surgery of the head and neck.

In 1895-96 he took a postgraduate course at the New York Eye and Ear Infirmary, and during the following year studied at the Central London Ear, Nose and Throat Hospital. From 1899 to 1901 he had private courses with Jansen at Berlin and at the Politzer Clinic in Vienna. Later he made short visits to American and European clinics.

In his early life he taught in the public schools of Indiana. His medical teaching began in 1889 as Lecturer on Pelvic Anatomy in the Central College of Physicians and Surgeons. He later became Professor of Physiology and Professor of Otology and Laryngology in the same institution. When the Central College became part of Indiana University Dr. Barnhill was made Professor of Otolaryngology and in 1923 he became Professor of Surgery of the Head and Neck as well.

Through most of his long life Dr. Barnhill was a familiar figure in the postgraduate teaching of anatomy in many of the short courses given by institutions over the country.

He was at various times President of the American Laryngological Association, President of the American Laryngological, Rhinologi-

cal and Otological Society and of the American Academy of Ophthalmology and Otolaryngology.

He was a member of the following associations: The Indianapolis Medical Society, the Indiana State Medical Association, the American Medical Association, the American Otological Society, the American Laryngological Association, the American Laryngological, Rhinological and Otological Association, and the American Academy of Ophthalmology and Otolaryngology. He was an honorary member of several societies including the Southern Medical Society and the Pacific Coast Ophthalmology and Otolaryngology Society.

In 1929 he was given an honorary degree of LL.D by Indiana University, and in 1934 was made honorary Professor of Anatomy at the University of Southern California.

He was the author of several textbooks on otolaryngological subjects and of a volume dealing with the American Revolution, entitled *Hatching the American Eagle.*

Even after he was largely incapacitated with arthritis, he made a point of attending the meetings of the societies whose progress had for many years played so large a part in his activities. He will be remembered chiefly for the interest and vitality which he managed to inject into anatomical subjects and for his graduate lectures on these themes.

American Board of Otolaryngology

The next examination of the American Board of Otolaryngology will be held in New York City at the Waldorf-Astoria Hotel and the New York Eye and Ear Infirmary on June 3-4-5, 1943.